FOOD AND DRUG ADMINISTRATION

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PILOT PROGRAM FOR STREAMLINING THE

LICENSURE OF BLOOD AND BLOOD COMPONENTS

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WORKSHOP

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WEDNESDAY

DECEMBER 9, 1998

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The workshop was held at 8:30 a.m., in the Plaza II Room of the DoubleTree Hotel, 1750 Rockville Pike, Rockville, Maryland.

SPEAKERS:

GILLIAM B. CONLEY, MA, MT(ASCP)SBB, Moderator
ELIZABETH CALLAGHAN, MS, MT(ASCP)SBB
MARY ANN DENHAM, MBA, MT(ASCP)SBB
REBECCA A. DEVINE, PhD
JAY EPSTEIN, M.D.
CAPT. MARY L. GUSTAFSON
LESLIE G. HOLNESS, M.D.
JONG-HOON LEE, M.D.

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:30 a.m.)

MODERATOR CONLEY: Good morning. Last chance to grab one more cup of coffee. There will be a break a little bit later.

Welcome to Rockville. If you had been here earlier in the week, it was so warm we're all having trouble getting into the Christmas spirit. I have a theory that it's because Texas was so hot last summer. It's like when you put a brick in bed with you to keep warm at night; it's still warming the whole nation. But we're getting there.

I'm the one who gets to introduce himself this morning. I'm Gil Conley, and I'm a Consumer Safety Officer in the Division of Blood Applications, and I'll be the moderator today.

Introducing myself, I kind of had a choice of deciding what to call myself, and I think moderator is probably best. I started with Master of Ceremonies, but then we would need candles on the tables, and I would have to tell jokes and maybe sing a song, and you would be sneaking out the back looking for the gambling tables. So we'll stick with moderator.

My task today is to introduce our speakers and to keep us focused on the task that we're here for. We really appreciate all of you coming to join

us. These meetings are always preceded by the disclaimers. The speakers today are all from the FDA, and they all have a vested interest in a smooth, efficient regulatory process which both protects and improves the public health.

Our other presenters today, hopefully, will be you, because we're presenting some new ideas and inviting discussion, and we hope that you'll participate in that discussion, especially later today; and, of course, you all also have a vested interest in the entire regulatory approach that the FDA follows.

Although the term workshop has really come to mean another name for a lecture series, that's not what we're about today. It's a true workshop where we want to exchange ideas, hear your thoughts and opinions on what we are currently proposing or thinking is a proper direction for regulatory affairs.

Why are we here today? Well, if you've heard me speak before, you know I like cartoons. They usually sum up life pretty well, and this one does.

In this one, Ruthie is coming home from school, and her grandfather wants to know what she has. She explains she has schedules, changes, and announcements for her mother, and she says, "I'm only in first grade, and already I'm fed up with the paperwork."

Well, there are a lot of us who feel the same way about some of the regulatory paperwork we've been through, and you've already seen that a lot of the changes that have been coming from our group in recent history have been geared toward reducing the paperwork, both for you to produce and submit and for us to review.

Today's efforts will, hopefully, extend that whole goal of reducing paperwork and easing the process without losing the FDA's responsibility for the public health.

Some housekeeping issues first: There are bathrooms right outside this door and more in the hallway around the corner. If you need to use a phone, again, farther down this hall on the right or back near the bathrooms over here there are phones.

Come lunchtime, there are many opportunities in the area. Of course, there is a restaurant in the hotel. There is a listing in your folder of local restaurants. Some are too far away, I think, for lunchtime, but directly across Rockville Pike in front of the hospital there's a Greek and Indian restaurant.

There's also more restaurants as you go up Rockville Pike, and if you exit through the door that's at the back of this auditorium and across the way, there's another restaurant on the right. You

won't have any trouble finding places to eat.

We also have a message center here today. In this day of cellphones and beepers, probably most of you won't need that, but in case you do need to give somebody a phone number where you can be reached today: 301-230-6757. That comes to a phone for the people who are manning our front desk area, and there is a message board out there that you can check during breaks.

You all got handout packages and, just briefly to go over some of the information that you'll find in the package: In the righthand pocket you'll find today's agenda. So if I deviate from the agenda, you can call me on it.

There's a list of our speakers, and there will be copies, I believe, of most of the presenters' slides to make it easier for you to take notes.

In the lefthand pocket there's a participant list, at least those who registered for the program ahead of time. It's possible there should be some people who are registering here today or that people registered and decided not to come, but that's the list of those who registered.

You will also find a sheet -- I believe it's on gray paper -- that is topics and questions for participant comment. We'll go over those in a little more detail later this morning, but they are some of

the issues that we want you to consider, and we specifically or especially want to hear your comments on this afternoon.

There's a sheet that describes the transcript that will be taken here today. There will be a full transcript of this meeting available 15 working days after the meeting. There will also be summary minutes that will be produced no later than 30 days after this meeting.

The easiest access for the transcript will be on the Net, and there's a Net address given to you on that sheet of paper. There are also other mechanisms for requesting a print, if you wish.

There are few sheets in there for notes, very few sheets. Write small. But there are also some cards in there that we'll want you to write your questions on. You may use those or later, as I said, there will be opportunities to come to the microphone.

Please turn your questions in after the speakers have spoken on the relevant topic. In past sessions we've found that we got a lot of questions that had to have been written before the speakers spoke, because the information was included in what they presented to the group. So after the speaker has completed their presentation, if you have questions, jot them down on those cards.

I'll be reading them. I'm getting older

all the time. We just got a stronger script. So please write clearly for me, and I'll organize those questions for later.

You can give those to me at the break or you can give them to the people at the front desk in the lobby or later in the day some of those same people will be circulating around the room to pick up your questions.

We will ask later this afternoon when you give your opinions to not limit yourself to just reacting to our own ideas that are presented, but to expand on them with suggestions and ideas for regulatory review.

Today's agenda -- There are -- Look at the agenda sheet with me just briefly. We've got large gaps of tim scheduled for breaks and for lunch. Please spend that time to sit down with your colleagues and, again, enhance the discussion so that you can share those ideas with us.

I think that's enough housekeeping. So our first speaker today is Dr. Rebecca Devine.

Becky is the Assistant Director for Policy for the Center for Biologics Evaluation and Research. She assumed this role in April of 1994 and has responsibility for the oversight of policy initiatives, regulation and guidance for CBER. In other words, she's an agent for change within the

FDA/CBER. She sponsors it, encourages it and, hence, meetings like this.

She's also responsible for the development and the maintenance of the managed review process at CBER. She's in charge of the system that keeps our reviews on track and on time.

Dr. Devine received her BS degree in microbiology in 1977 and a PhD in microbial physiology in 1986, both from the University of Maryland. She's held various positions in CBER in the areas of quality control testing, GMP review, inspections, and vaccine and biotech application review since she jointed the FDA in 1979.

Becky is here from the Office of the Director to welcome you.

DR. DEVINE: Good morning, and welcome to the workshop. As Gil said, I'm here to welcome you, and I would also like to thank those of you who have taken the time out of your busy holiday schedules to come and spend some time with us.

I think it's important, as we go through our reform initiatives, that we get feedback from the regulated industry and the affected public. So that's why we spend time and effort to have workshops such as this, to get that kind of feedback.

In terms of setting the stage, in 1994 in January, as you all may recall, we issued a Federal

Register notice asking people to give us input on where we could change our regulations. This was part of an effort that we were taking to look at all of the biologics regulations and decide where they needed to be changed if they were outdated or were no longer useful in terms of what we wanted to accomplish to protect the public health.

We got many comments during that time period, and in addition to that, we specifically queried the blood industry for ways that we could change the blood regulations. We also received much input on that.

Over the past four to five years, we have been embarking on an effort to accomplish many of these changes. In 1995 we began our reinventing government initiatives under Vice President Gore's leadership in terms of how we could streamline the regulation of medical devices, drugs and biologics.

As you might recall, in April of 1995 we issued our first RIGO report which indicated some of the initiatives we were undertaking. One of the very important initiatives that affected the blood industry in that time period was the manufacturing changes streamlining that we were undertaking.

In that time period, April of '95, we issued our first effort in terms of trying to downgrade certain types of manufacturing changes.

That was just a first step. We, after the guidance, had to go forward to change our regulations at 601.12, and that effort was completed in July of 1997.

Now during the comment period for the manufacturing changes rule, it was interesting that we did not get a lot of public comment on the proposed rule and the attached guidance documents. However, after the comment periods had closed and we were now working on the final rule and issuing final guidances, we then began to hear some dissatisfaction with some of the initiatives.

So we thought we had made great efforts to try and get the input during the comment period, and that's again more of the reason why we're here this morning. It is helpful for us to know ahead of time. So please don't be shy about giving us your input on this proposal that we're talking about today.

Now in terms of the other initiatives that have affected us and that are moving us towards this, we have, obviously, been affected by the passage of the Food and Drug Administration Modernization Act which was signed into law in November of 1997.

Now that law codified our second RIGO initiative, which was the elimination of the establishment license application and the product license application, and our moving to a single biologics license application for all biological

products that are subject to licensure under the Public Health Service Act.

Now we have not yet been able to complete that initiative, but we're getting very close. We proposed a rule, and we had an open public meeting in September to discuss that. The comment period on the rule has now closed, and we received several letters of comment.

It's interesting that most of the comments we received were from the blood industry. So for those, I thank you, and we are now working on trying to get that rule finalized.

The companion document to the proposed rule was the CMC or the Chemistry Manufacturing and Controls guidance document that described what information would go into the BLA. Now it proscribed a set of things we thought were appropriate for inclusion in the BLA, and we are now currently evaluating comments on that as well.

Now as you know, there are many oversight bodies which are looking at how we regulate blood and other biological products. As a result of many of these oversight reviews, we have established in the Center a blood action plan to address many of these public health issues that have been brought to our attention in some of these oversight, as well as to address the reform efforts that we were undertaking

starting in 1994.

Part of the blood action plan is this effort at the pilot program which we will be talking about today. One of the things we're trying to do is look for areas where the amount of information that's submitted in an application can be streamlined or decreased as much as possible.

So we're now talking about proposals such as the one today where we would submit less information, and we would be able to approve, hopefully, applications on supplements more quickly and streamline the process.

So, hopefully, that's put the effort in perspective for you, and again the only way that we can really make this useful for the industry is to get your feedback.

So I really hope that we get a good dialogue going today. I notice there are many FDA people that deal with the regulation of the blood products in the audience, and they're very anxious to hear your thoughts.

If you are shy and you don't want to step up to the microphone today, there are other ways that you can give us your input. The guidance document, which will be discussed today, was posted on our Web site. It is available there for people under our FDA/CBER guidelines location on our Web site.

In several weeks there will be a Federal Register notice of availability for that document that we'll publish, and it will have a docket number, and that would be a place where you could send written comments to the document, if you feel that you really don't want to get up to the microphone today; but I would encourage you to come to the mike today. don't be shy. We really are very anxious for your input.

I hope that we have a productive meeting. We have a lot of time scheduled today, and the success of the effort today is going to depend on participation from the audience.

In terms of my recommendations and wishes for you today, I hope that we have a productive meeting and get lots of good input. My recommendation for lunch is Ambrosia, and I would order the gyro platter. So have a good meeting, and thanks for coming.

(APPLAUSE)

MODERATOR CONLEY: Any program that runs absolutely on schedule must be boring. So we have a surprise welcome not on our agenda. Dr. Jay Epstein is the Director in the Office of Blood.

If you understand the organization of the Center, there are a number of offices within the Center for Biologics, and Jay heads up one of those groups and wants to re-accent how welcome you all are

and how much we appreciate your time today.

DR. EPSTEIN: Thank you, Gil. The moderator said, well, if you're going to come, you're going to speak. So --

Let me just express my pleasure in being here and having the opportunity to greet you all personally, and to add my appreciation to those that you've heard for your willingness and interest to come today and help us in this task.

I'm sure you all know the Chinese proverb that a journey of a thousand miles begins with a single step, and this fairly small and fairly quiet meeting really is the start of what potentially is a major new approach to blood licensing.

As Dr. Devine explained, the FDA is responding to a set of forces. We are highly mindful of our responsibility to assure blood safety and availability. At the same time, we live in an era of cost accountability and downsizing, and there is a need to streamline, both for the purposes of the FDA and for the purposes of the industry.

I cannot overemphasize the fact that success in this endeavor depends upon you and your colleagues. We think that it is essential that we engage in a good, two-way communication, and we certainly hope that you and your counterparts will embrace this initiative constructively and make it

work.

What can you do? Well, you can help us spread the word, and you can set good examples of successful use of applications through monographs. What you need to know is that the agency is poised to move fairly quickly to expand the scope of the use of monographs, should the pilot demonstrate that this is a successful mode which results in safe and effective products.

So I would encourage you to interact fully at the workshop. Otherwise, let me just say that I hope that you have a fruitful day and truly enjoy this "inside the Beltway" experience.

(APPLAUSE)

MODERATOR CONLEY: So you're only a small group today, and you've already heard how important you are and what a role you may get to play in setting the tone for future changes in regulatory review.

Our next speaker, Captain Mary Gustafson, is the Director of the Division of Blood Applications in the Office of Blood, CBER, within the FDA. That means that the majority of the people who are coming to the podium today report to Mary, and she shepherds our efforts within the Division of Blood Applications.

It's a little bit like harnessing the potential energy in a rock slide to good use, but that's what she does.

During her career with FDA, she has been involved in policy development, product approval, and compliance enforcement in the regulation of biologics, but primarily in blood and blood related products.

She frequently speaks to the blood and regulatory organizations concerning FDA's regulation of blood. She's a registered medical technologist and a blood bank specialist, and prior to coming to the FDA she worked in clinical blood banking for several years at private hospitals and then at the National Institutes of Health.

She holds a BS from Fort Hays State University, an MS from University of Tennessee Center for Health Services. She is a commissioned officer in the U.S. Public Health Service.

Mary will discuss the background issues which have led to today's meeting to discuss possible new regulatory approaches. Mary.

CAPTAIN GUSTAFSON: Thank you, Gil. I loved the introduction. I think I would refer to my job not like a landslide. I usually think it's more like herding cats. Also, listening to my bio, I know I have a dilemma, having received my Master's degree from University of Tennessee, and I have a daughter who's a sophomore at Florida State. So the Fiesta Bowl this year is going to be a real dilemma for me.

The primary reason that we're here today -

- By the way, I have six or seven overheads. They're not in your packet, but they're not anything that's critical to the actual program. So you may wonder why in the world I'm even speaking. It truly is background on why we have gotten to this point in blood licensing.

The primary reason is that licenses are required for blood and blood components when they cross state lines. Up until about a year ago -- in fact, for nearly two decades in FDA -- I would quote the language of the Public Health Service Act as saying no person shall sell, barter or exchange from any state into any other state any biological product unless that product has been manufactured at an establishment holding an unsuspended and unrevoked license.

As Dr. Devine mentioned, there is a law that was passed in 1997 that's called the Food and Drug Administration Modernization Act. Among many other provisions that we are grappling with, it changed the language of the Public Health Service Act, so that it reads more like the language in the Federal Food, Drug and Cosmetic Act.

That is, "No person shall introduce or deliver for introduction into interstate commerce any biological product unless a biologics license is in effect for the biological product."

You may ask, what in the world does that wording change mean? Well, it eliminates the need for an establishment license altogether. It has some more subtle meanings that I will leave to the attorneys for another day, but the bottom line is that a license is still required when a biological product crosses a state line.

In the past few years we have been working on changes in the way we license biological products to decrease the burden on industry, which is you, but still ensure the protection of the public health. One of the changes was initiated as a report reduction project and ended up as a change in the regulation governing when and how changes to an already approved product are reported to the FDA.

This is a change in the regulation covered by Title 21, Code of Federal Regulations, Section 601.12. The new regulation was enacted in July of 1997 and implemented in October of 1997.

Reporting of changes was stratified by risk into three reporting categories. Changes to an application determined to have a substantial potential to have an adverse effect on the product requires the submission of a supplement that must be reviewed and approved prior to the product prepared by the changed method being shipped for use.

Changes to an application determined to

have a moderate potential to have an adverse effect on the product require the submission of a supplement, but product manufactured by the changed method can be shipped prior to the submission actually receiving approval.

Changes that have a minimal potential to adversely affect the product can be reported once a year in an annual report. The report is reviewed and filed in the license application, but the changes reported in this manner are not issued an approval. This change in reporting was undertaken to benefit both the industry and FDA in terms of reducing the reporting burden.

We have quickly learned that use of the prior approval supplement route assures the greatest public health, but is basically the status quo of how applications have been submitted, reviewed and approved over the years.

The 30-day changes and the changes being effected upon submission -- that is, the CBE-30 and the CBE -- may benefit the industry somewhat because of the ability to implement the change and ship the product prior to the approval being granted. However, this reporting category does nothing for us.

In fact, the need to review the submission upon receipt to determine if the reporting category is correct requires us to track these submissions

separately and increases our burden. We also know that you in the industry are not terribly comfortable with the notion of going ahead with a change without knowing for sure if it is approvable or not.

The annual report, although viewed by many of you as a new burdensome reporting requirement, is where we see the most regulatory relief. We have been impressed by the reports we have received in terms of the reporting being in the correct category.

There have been few cases in which we have disagreed that the change was not minimal but had either a moderate or a substantial potential to harm the product being changed and, therefore, should have been reported in a higher reporting category.

We know that we owe you additional guidance for reporting under 601.12. You have told us that you wanted the blood and components guidance removed from the general biologics guidance, because so many of the examples are not related to what you do, and the language is, well, rather druggy.

We have been preparing the guidance you want, but quite frankly, we want to include as much as we can in the annual reporting category, since we think this category benefits all of us. We are looking for as many changes as possible that represent a minimal potential for harm to include in the guidance document.

Another change that was begun several years ago for a group of biotech products and made into law by the Food and Drug Administration Modernization Act of 1997 or what we call FDAMA is the elimination of the establishment license application and establishment licensing and the replacement of the product license with a biologics license.

Currently, we are in a transition period. Since February of this year when FDAMA was implemented, we have issued biologics licenses, but have issued those licenses based on the review and approval of separate filings for the product and the establishment.

Yeah, I know it's really confusing. If it's confusing to you, you should know what it's like to work with it on a day to day basis. We have numerous internal discussions about where we are and what we are doing in relation to biologics licensing. Most of the time I feel like I'm in a very bad revival of the famous "who's on first" sketch.

Sometime in the near future, we will be implementing the biologics license application. The enactment of FDAMA in many ways put the cart before the horse in terms of our planned implementation of the biologics license application process.

During the summer, we published for comment a guidance to assist manufacturers in the

completion of the biologics license application for blood and blood components. The agency, as Dr. Devine mentioned, also published a proposed rule o regulation changes to accommodate the biologics license application filing.

Comment periods for both the guidance document and rule have ended, and although we did not receive a lot of comments, we are thoughtfully considering each one and making revisions as necessary.

When the guidance publishes in final, we wills be ready to accept applications filed using the Standard Form 356h, which is an application form that will be used for all drugs and biologics. Those of you who have approved product and establishment licensed applications will be automatically deemed to have an approved biologics license application, which can then be supplemented with a single application filing.

In addition, the group of common products that currently have separate license applications will be consolidated into a single filing for blood and blood components rather than the separate product filings.

We believe the change to the biologics license application filing will reduce the filing burden to industry. We do not know what economies we

will actually derive from the change.

Our work in preparation for the change, including guidance, tracking and document handling, have been very resource intensive for us. We plan for the payoff to be in less administrative paperwork once the filing change is implemented.

The process changes I have just mentioned were discussed in detail at our workshop almost exactly one year ago today. Staff members from the Division of Blood Applications also presented these changes during a workshop at the American Association of Blood Banks annual meeting in Philadelphia this year.

In addition, I know that there have been considerable one-on-one discussions between you and your consumer safety officers concerning these changes.

I am also, as background for this workshop, going to share with you some information about our performance in the review of blood and component applications and our resources.

We currently function under a managed review system. By managed review, I mean the applications and supplements received for review are assigned to a reviewer or a team, tracked, assigned a review goal, sometimes with interim milestones, reviewed against an internal SOP, and checked by

supervisory staff for regulatory and scientific quality.

Reviewers are accountable for the quality and timeliness of their reviews. Review performance goals and measures are determined as part of Vice President Gore's National Performance Review. The initiative is Government Performance Review and Accountability or GPRA.

Currently, for blood and blood components, the GPRA goals are 12 months for the review of new applications and substantial supplements and six months for lesser supplements.

Now I know you think these times are too long. I was born at night but not last night. However, before you storm the podium, let me show you our performance data over time.

First I want to show you our application submission inventory by years. The fiscal year is represented along the x axis. We are on an October to September fiscal year. So for us here in the government, 1998 has already ended.

The y axis represents the number of submissions. I have lumped the received submissions and the pending submissions together, since they represent our in-box, and they are represented by the shaded box.

The solid blue bars represent the

submissions completed during the year. As you can see, our in-box grew in the early 1990s, while our completions remained fairly constant.

What happened in 1995? The big jump in received and pending submissions was due, in large part, to the licensing of irradiated blood components. However, in 1996 the in-box was substantially reduced, and this continued into 1997.

I am somewhat concerned about the lower number of completions in 1998, with the flatlined received/pending column, and I'm looking into the reason for this. At this point, I'm not sure if it is due to staffing, implementation of the revised 601.12 regulation or perhaps other reasons.

One reason may be that we have just simply hit the critical mass in workers, and I'll show you a later slide on that; but is a marker for concern, if it continues into our current year.

My second overhead shows you our time to completions over time. Once again, the fiscal year is horizontal. The months to completion are represented vertically. I have split the original applications from the supplements to approved applications.

Applications are blue, and supplements are yellow. I have chosen to represent median time to completions rather than averages, since they seem to be less skewed by outliers. I have also chosen the

cohort of submissions completed in the year rather than the cohort of submissions received during the year.

This is because the 1998 and some of the 1997 submissions have not yet been completed, or those that were received in those years, and hence those datasets are incomplete, and they would be, consequently, misleading, which is good enough for the President. It's not what I want to do, though.

As you can see, over time our completion times have generally decreased. The GPRA milestones were first established in 1997 using 1996 data. You can see from the graph how 12 months and six months were established as reasonable performance goals from the 1996 data.

These goals were not changed last year, even though our performance had improved, in large part because of the planned institution of the biologics license application and the changes to our system, including our computer system, that had to be done in order to accommodate the new filing system.

The bottom line was I was just plain scared silly that we would not be able to meet our review performance, knowing how many of our review resources were being used in planning for the biologics license application change, but as you can see, in 1998 our performance still improved.

In 1998 our median time frame for review of new applications was six months, and our review of supplements was just under four months. I am very proud of my staff for their efforts in reducing the time to review applications.

As I mentioned when I showed you the earlier slide, however, I am somewhat concerned about the pending versus completion ratio from last year, and will be monitoring that ratio.

My next overhead compares the number of completed submissions versus our full-time equivalent or FTE personnel resource burn. The FTE burn is calculated from our resource reporting system. Periodically, a reviewer reports how he spends his week. This information is generalized for the entire year.

The fiscal years are across the bottom of the graph, as in earlier slides. Along the left vertical is the number of completions. Along the right vertical is the number of FTEs used in the effort. The blue bars represent the completions and correspond to my first overhead blue bars. The orange line represents the full-time equivalents that it took to perform the application reviews.

I limited the FTE burn to application and supplement review only. As you can see, in 1992 15-plus FTEs completed fewer than 500 licensing

submissions. In 1998, just more than six FTEs completed nearly 700 licensing submissions. It shows that we are truly doing more with less.

The drop in FTE burn is due to a couple of factors. One, we have fewer people assigned to the work unit that reviews blood and blood component licensing submissions than we did in the past. We have had some downsizing in this area over the past few years, but also the staff we have are being asked to do a greater variety of operations.

The reviewers are not just doing reviews. They are developing policies, performing pre-license inspections, training and providing guidance to industry and FDA field personnel, working on initiatives for change within the Center, and probably dozens of other things that I can't think of right now.

So what does this mean to you? I know, you're looking at the 1992 FTEs and thinking, all she has to do is get back those 15 FTEs, and they can approve my application filings before I even put them in the mail. So let's all pack up, go to lunch, and spend the rest of the day shopping.

Now I have to burst your bubble and show you why we think we have to make even further changes in the licensing process in order to provide reasonable service to you, while protecting the health

of recipients.

I borrowed the next set of overheads from Mr. Mark Elengold, who is the Center's Deputy Director for Operations, hereafter referred to as the party pooper.

The first overhead in this series is what Mark refers to as the flying wedge. Once again, the years are across the bottom. On the vertical line, this time we have money in millions of dollars.

S&E is government language for salary and earnings. The red area represents how much money we were appropriated in the salary and earnings category of operating funds. This is where our people money comes from.

The black wedge represents how much money we would need to remain in a constant operating level. As you can see, it goes up ever so slightly over time. This is because "constant' is not really a flat line, because everything costs a little bit more now than it did in 1995.

Once again, the bottom line is that, in order for CBER to maintain our operations as they were in 1995, we would need roughly one-third more money than we have right now.

I am sure that you could show me similar representations for your own institutions. This is not unique, but it is a problem.

The next overhead breaks down CBER's operating allotment further into personnel monies under the prescription drug user fee program, called PDUFA, and monies for personnel in the non-PDUFA programs. I will not go into much detail, but PDUFA programs are those that are funded by money paid by drug companies to review their applications.

These allocations are protected by law in that money paid for the review of these applications cannot be diverted into other areas.

As you may have guessed by now, blood and blood components are not covered under the Prescription Drug User Fee Act and are non-PDUFA. On the graph, the non-PDUFA S&E base is represented by the aqua line at the bottom of the bar. As you can tell, the aqua line is getting smaller and smaller and smaller.

The last overhead represents the total CBER allocation of funds broken down by operating dollars versus payroll. Even with a constant number of employees, which we haven't had, the payroll money increases due to promotions and cost of living increases, and the President has just announced the other day that Washington area Civil Service employees are due, I believe, a 3.68 percent increase in January. That increase comes from our allotted funds.

Since the Center does need operating funds

beyond payroll, the only way to avoid cutting into the operating funds with the increasing payroll is to decrease the number of employees.

The Center's allocations are not going to increase. PDUFA funding is protected. Employees need their promotions and cost of living increases, and therefore, the staffing dedicated to the non-PDUFA review programs will keep decreasing.

This is why we are here today. We can keep doing what we are doing with fairly minor streamlining changes, such as the changes in the requirements for reporting changes to approved applications and the BLA implementation, manage our submissions under a pretty effective system of managed review and accountability, and still have you unhappy with us, because we will not be able to decrease further our review times and likely will increase our pending backlog; or we can float a trial balloon for a new licensing paradigm.

Yes, I hate that word, but it was the only thing that I could really think of to fit what we're doing.

Today we are going to present to you our ideas for licensing under a program of self-certification to a monograph standard. As Gil mentioned, we want this to be an interactive process, and Dr. Devine and Dr. Epstein also, I think,

mentioned that to you, that this is very important to us. We want and need your input into this concept.

Do you support or feel a self-certification licensing program would be useful and effective? We want your input on the specific areas that we have chosen to pilot.

One is designed for the blood bankers and involves licensing of irradiated blood components. The other is designed for the source plasma community, and addresses red cell immunization programs when the red cells are obtained from an already approved source.

The draft guidance for the irradiated blood program is hot off the press, and you were given a copy. It's on the Web, and it will soon publish for comment.

The other draft pilot guidance is not yet released. You will have to listen carefully to the presentation to see our proposed strategy for conducting this pilot.

We appreciate your coming to this workshop. We are looking forward to your comments and help in developing these pilot programs. Thank you very much for your participation.

(APPLAUSE)

MODERATOR CONLEY: Just like the review turnaround times that Mary showed you, the FDA is

getting shorter and shorter in its schedule. So we're a little bit ahead of schedule, and we will take that time in hopes of maybe letting you out sooner for lunch so that you can go to one of these nearby restaurants.

So we'll take a half-hour break now. Through some fluke in hotel package deals, we actually have refreshments. Please don't expect them at the next FDA meeting. However, we will reconvene at ten of the hour. Thank you.

(Whereupon, the foregoing matter went off the record at 9:23 a.m. and went back on the record at 9:53 a.m.)

MODERATOR CONLEY: Mary told me that she had intended to tell a joke, but then forgot to. After her slides about the reductions at FDA in our support, she wanted to explain that, when I first started to work at FDA, I used to wear full-length ties.

We're starting to get into the meat of today's presentations. So pull out your pens and sharpen your pencils, and start to think about your comments, how you feel about the information that's being presented.

Our next speaker is Dr. Jong Lee. Dr. Lee is the Branch Chief at the Division of Blood Applications. He's been at the FDA approximately

three years. Jong will discuss the basic concepts behind the possible new regulatory approaches. Jong.

DR. LEE: Good morning, and welcome. I'm really glad that I was here on time to listen to Mary's presentation. That explains to me why I've been having so much trouble over the last several years, and it gives me renewed confidence that I'm doing the right thing. However, we are here to propose to you to do even better.

If I could have the first slide now -- We have heard a fair amount of general background material thus far, and those are very important points that were made in the background presentations.

Now we are beginning to delve into the specifics, and mine will be the most general presentation of the specifics of the pilot program that we'll be describing to you. I will focus on general basic principles, and I hope my presentation will give you a solid background to listen to the specific pilot programs that are to be described in a few minutes.

As in the way of brief overview, this is the listing of the ten basic concepts that I'll be discussing. By now you've heard from our previous speakers about the fact that this is an interactive workshop, and we need your input in telling us that we are going the right direction.

The first concept I will be discussing is that of self-certification and how this pilot program hinges on the idea of self-certifying to a set of CBER-prescribed guidance documents. I will explain then the difference between the pilot versus the pilot program, and there's a distinct difference.

I will explain how we propose to use this pilot within the pilot program as the new licensing mechanism, and I will go over how the pilots, specific pilots, and the pilot program fits in with the BLA and changes to reported streamlining initiatives.

I will go over how all of this falls under good guidance practice and that the proposals that we make today are not effective, but will be according to good guidance practice provisions.

I will make a comment or two about modifying the guidances or the inability to modify the guidances, to be more specific. I will then go over the legalities of how the pilots have to be conducted as a variance request, and I will end with two comments about evaluating the pilot and expanding the pilot to be of more general applicability.

I have organized this presentation into a series of ten basic concepts, and basic concept number 1: We have been given the charge -- By we, I mean the Blood and Plasma Branch within the Division of Blood Applications -- to define the CBER pilot program to

streamline blood licensure, and our group chose to do this through an interactive dialogue with the regulated industry.

These are the current efforts already in progress in terms of streamlining, and there's the team blood and team biologics efforts that you've probably heard about, and these refer to the inspectional efforts. But in terms of submission review and with specific to licensure, you've already heard about the biologics license application initiative and changes to reported initiative.

With respect to blood and blood components, these two major licensing initiatives will be in the near future, we hope, supplemented by yet another streamlining initiative that we call the pilot program at this point.

So in terms of workshop goals, we propose to describe the new pilots, and there are two, to be specific, and we propose to describe them in terms of the overall pilot program which encompasses these two specific pilots.

We hope to engage you, and we hope to make sure that this is an interactive workshop, having a lot of ample time for question and answer sessions as well as discussion panels; and we invite you to write in comments, if you aren't able to provide them to us verbally at this workshop.

So having impressed upon you the fact that this is an interactive workshop, let me move on to basic concept number two: An applicant may self-certify adherence to CBER licensing criteria as outlined in a Pilot guidance, in lieu of submitting a conventional application that includes detailed standard operating procedures.

What do we mean by self-certification? We mean self-certification to a specific guidance that is released under the pilot program, and we hope to write these guidances in such a way that these are SOP oriented -- in other words, that they readily lend themselves to a conversion to a specific standard operating procedure that fits your center.

In a sense, these guidances that are SOP oriented are, in a sense, pre-reviewed by CBER. The traditional paradigm has been to submit -- to make a submission that describes the standard operating procedures and then review them and approve them.

In a sense, we propose to reverse the process. We have already reviewed, because these are -- this SOP oriented guidance document has been released by CBER, and your self-certification that you adhere to that would then simply constitute -- would simply constitute the submission. You're telling us that you have now adhered to the "pre-reviewed" guidance document, which allows us to simply proceed

with the next step of the review and, in these two specific pilots, the inspectional process.

This idea is not really new. This has been discussed widely among the industry in the past, and the American Association of Blood Banks has proposed in the past that we release FDA checklists, and we have done this, but we haven't quite encompassed the idea of their self-certification to the checklist as being enough for the licensure process.

The American Blood Resources Association has urged the agency in the past to write and release standard SOPs, so that they can simply submit the SOP that was written by the agency which would obviate the need to review them.

So what we are proposing today is sort of in between the two concepts already proposed in the past by the regulated industry. We are taking more of a detailed approach than simply releasing a checklist. However, we are not going so far as to actually write detailed standard SOPs, recognizing that true SOPs can only be written to fit individual centers.

Okay. So the whole cornerstone of the pilot programs is to self-certify to a previously established guidance document, and previous speakers have alluded to them as monographs. Whether it be called monographs or guidance documents, we mean

something written and released by CBER to which you can self-certify adherence, which would then allow us to move towards the next phase of evaluation -- that is, inspection.

Moving on to basic concept number three, the two pilots to be described in detail today are specific proposals under a broader, more slowly evolving pilot program. How do we define the pilot program?

Well, for now, pilot program centers around the idea that we are using guidance or monographs in lieu of detailed review of standard operating procedures. The pilot program is a broader concept than the specific pilots.

Then what are the specific pilots under the Pilot Program? We defined specific pilots as well defined regulatory areas, and these areas is to be defined by a specific guidance released under the Pilot Program or pilot guidance.

Today we are here to discuss in detail the irradiation pilot and the red blood cell immunization program pilot by two speakers following myself.

In trying to define the Pilot Program and the specific pilots, it's difficult to have everything mapped out right from the beginning, and the Pilot Program was defined by the idea of self-certification to a previously established monograph or guidance, and

that was enough of a long term goal to allow us to begin to think about the specifics.

Then how do we define the specifics? How do we take the first step towards this overall program goal? In trying to establish which areas to target, we had to take a step back and think about what the specific areas should fulfill to serve effectively as pilot candidates.

Whichever area that is selected, the regulatory area has to have some measurable outcome. That is, what is the impact of omitting review -- up-front review of detailed standard operating procedures? That effect has to be measurable.

In addition, whatever is learned from having conduced the pilot, that outcome should be of enough general applicability to be able to be of use in different settings other than the pilot itself.

Thirdly, we have to have enough resource to conduct the pilot and, hopefully, to expand the pilot to other areas for the whole thing to have practical implications and to be of true practical benefit.

Fourth, we would like to have the areas selected for the pilots to have some limited public health impact. In other words, we don't want to target an area where the implications for public health is too great.

Lastly, although we want to have limited public health impact, we want the public health impact to be enough so that there is sufficient interest in moving forward with the pilots. In other words, we don't want too much risk, but we don't necessarily want too little risk, because risk is almost always tied in with the interest level of the applicants.

In trying to come up with areas that fit those criteria, we took a look at the current way of reviewing and approving license applications. For a typical new license application, currently the establishment license application and the product license application, a detailed submission is reviewed, and then it is followed through by a pre-license inspection, and submission plus the inspection constitutes the entire review process.

For changes, manufacturing changes, to be reported to the license, once the license has been approved, it is done by a supplemental application. Typically, the supplemental application consists only of the submission only, submission without the pre-approval inspection.

There's two noteworthy exceptions to this current way of reviewing and approving license applications, and that is in reviewing the irradiation supplement and the red blood cell immunization program supplement.

Although these are supplements, the way that is reviewed parallels more closely that of the new license application. That is, a detailed submission which includes detailed standard operating procedures are reviewed, and then it is followed by a pre-approval inspection before a decision is made on the approvability of that application.

So irradiation and red blood cell immunization programs are exceptions in that they are supplements. Yet they are handled more like new license applications in terms of review elements.

It also just turns out that the Gamma irradiation supplement falls in the area of transfusion components; that is, components that are intended for direct transfusion into humans. We have used the memorandum issued in July of 1993 as the starting point from which to develop the specific pilot guidance that will serve as templates, so to speak, for you to use in converting that to a specific standard operating procedure, suited specific for use at your center.

Mary Ann Denham, the Consumer Safety Officer in the Blood and Plasma Branch, will go over this in detail. She has extensive experience as an inspector, as well as a reviewer, and she is regarded as the internal expert on the subject of Gamma irradiation of transfusion blood components.

The second area that jumped out at us from looking at how we review license supplements now is the red blood cell immunization program. Nicely, this represents -- This could be considered as the pilot, specific pilot targeted for the source components industry.

Although these are both blood components, source components are conceptually different from transfusion components in that these are components that are intended for further manufacture into other blood products or blood derivatives, and they are not intended for direct human transfusion.

So even though they look the same in terms of a physical product appearance, their intended use is entirely different and represents a -- the source industry represents a regulated industry that is distinctly different from transfusion components industry.

So, fortunately, review of the current ways of looking at license applications revealed two areas and, fortunately, the two areas happened to respectively lie in the source area as well as the transfusion area.

Similarly as in the Gamma irradiation topic, we have used the March 1995 memorandum on the subject on red blood immunization program as a starting point on which to build a specific guidance

to be released under the pilot which will serve as a template for you to convert into a specific operating procedure for your use.

Because CBER has written this pilot guidance, or will write the pilot guidance, we consider these as "pre-reviewed," allowing us to move directly into the inspectional phase of the evaluation and omit the detailed review of the standard operating procedure.

Elizabeth Callaghan, prior Consumer Safety Officer in the Blood and Plasma Branch, who also has extensive experience as inspector as well as a reviewer, will go over this topic with you, and she is our undisputed expert on red blood cell immunization program internally.

Now I should say one more thing about the red blood cell immunization pilot. The red blood cell immunization program basically consists of three major areas, the cell qualification area, the donor immunization and donor monitoring.

For purposes of the pilot, we have decided not to consider the cell qualification area, for two reasons. Firstly, the cell qualification process has a mandatory two-year quarantine period or at least one year, depending upon exactly where you are in the qualification process; and because of that mandatory quarantine period, we felt this to be of relatively

little interest for those interested in gaining time by not having CBER perform an up-front review.

Secondly, our prior inspectional experience has revealed that including this in the pilot would pose a public health risk that is more than what we are willing to accept at this point.

So based on considerations of public health risk, in turn based on our prior inspection experience, and because of the obligatory quarantine period associated with the cell qualification, we have decided not to consider this portion of the red blood cell immunization program as part of the red blood cell immunization pilot, and the pilot itself will then focus on these two areas.

So reviewing the current ways of license application evaluation generated two obvious areas to consider, and applying these five major criteria of measurability, generalizability, resource considerations, public health impact, and interest level has confirmed that these two areas, which readily lend itself to pilots, based on the current ways of reviewing applications, as two best candidates for the specific pilots to be initiated under the broader Pilot Program.

How well do these fit the criteria? We feel that, because of the inspectional element associated with the two supplemental applications,

that the outcome under the pilot will be imminently measurable through the inspectional findings.

How generalizable are these findings? That's a difficult question. However, recognizing that the transfusion components industry and the source component industry are really two separate worlds, however, within each world that the general operational concepts are similar, and we feel that having broken up into two separate areas that the outcome -- the experience that we gain under the Pilot Program will be, at least to some extent, generalizable and allow us to move forward to the next phase of the pilot.

What about resource considerations? We feel that, in terms of the Gamma irradiation pilot, that most blood centers interested in obtaining a supplemental approval for irradiation has already received them.

As Mary pointed out in previous presentations, the huge peak in 1995 was because of that, and that that peak has come and gone. However, there is still a steady baseline level of applications for Gamma irradiation, but that steady baseline level is a level that we feel we can handle with current resource allotment. However, we feel less sure about our resource considerations in terms of the red blood cell immunization program.

Our prior inspection experience has revealed that the inspectional process can be quite tedious, and the level of requests for red blood cell immunization program is at a level such that this makes us feel a little bit uneasy about our resource levels.

What about the public health impact? Again, our prior inspectional experience has revealed that this has truly limited impact, and that the industry is -- the understanding about the Gamma irradiation among the industry is such that we will not have too much concern in moving ahead with the irradiation pilot. However, again based on our prior inspection experience, we feel less certain about that, but having removed the cell qualification aspect of the red blood cell immunization program from the pilot, we feel more confident that this can be converted to an X.

What about interest level? Well, the same reason that limits the public health impact also lowers the interest level, as we anticipate. However, for the same reason of the concerns about resources and public health impact is the very reason that we feel that this is probably of reasonable interest from the industry.

So the two areas that we target are not perfect. However, this is as best as we can get, and

these are the two areas that we propose to you for in depth consideration today. So we are 30 percent done.

Basic concept number four: For each specific pilot under the Pilot Program, the viability of a new licensing mechanism will be tested. By now, I hope it's clear to you the difference between the specific pilots and the overall Pilot Program.

The pre-licensing inspection is the cornerstone of the two pilots, and that is the component of the pilot that allows us to assess the impact of conducting the pilot.

The pre-licensing inspection is to be conducted within 90 days of your self-certification to us that you adhere to the CBER prescribed guidance documents released under the Pilot Program, and it allows us to assess two things.

It allows us to assess the ability to self-certify. It allows us to assess your ability to self-certify, and this is an assessment at the individual application level. In addition, it allows CBER to assess the suitability of that particular area as a pilot candidate.

Basic concept number five: The two pilots are consistent with the existing biologic license application and changes to be reported streamlining initiatives.

You've already heard in some detail about

the BLA initiative and the changes to be reported initiative, and many of you probably have attended the full blown workshop last year on the same subjects. Here I would like to simply call your attention to how the two specific pilots that we propose today fit in with these two streamlining initiatives.

Now these are targeted for the specific pilots and not the entire Pilot Program. As the Pilot Program evolves, the relationship of how all of this fits may change, but we cannot do everything at once. We have to do things one step at a time.

We have an overall Pilot Program goal of self-certification, and how we implement that as a first step is the challenge here. Therefore, I have chosen to depict the relationship only for the specific pilots as it fits in the overall scheme of things.

What's shown in red is what's current and currently in effect, and what's shown in green is the future. We are currently operating under ELA and PLA licensing mechanism, and we are currently in a transition period to move over to the BLA initiative in the future.

The entire changes to be reported initiative -- I called it initiative, because that was recently changed, October of 1997, by adding new reporting categories, the changes to be effected in 30 days, the

changes to be effected immediately, and the annual report mechanism, in addition to the already existing prior approval supplement mechanism.

This changes to be reported mechanism is already in effect, and the prior approval supplement is one category, one major category, under the changes to be reported licensing mechanism. What we are proposing are two pilots that fit in as options to the traditional ways of reporting prior approval supplements.

Just to look at this in a different way, the changes to be reported mechanism consists of three major elements, if you were to combine these two as one, three major elements: The prior approval supplement, the changes to be effected in 30 days or immediately or the annual report mechanism; and those categories are arranged according to their level of public health risk.

With low level of risk or at risk that we consider to be minor of public health impact, we have chosen to use the annual reporting mechanism where you can simply report to us what you have already done within the past year. Of course, if we happen to pick out some problems or questions, we will be in communication. Otherwise, you will not hear from us.

The changes to be effected in 30 days is basically the intermediate level where you will tell

us that you are going to do something either immediately or in 30 days, which gives us the ability to intervene either very shortly after or before the actual implementation of your proposed change.

We have chosen to use this mechanism for items of moderate public health impact. But we still rely on the prior approval supplement mechanism, and this mechanism, obviously, is targeted for those areas that we consider to be of major public health impact.

The sizes of circles here is chosen just to give you a qualitative idea of the number of supplemental applications that we receive under each category. By and large, the majority of the supplemental applications that are received still consists of prior approval supplements, although this -- the sizes of this circle here is increasing every day.

Now if you were to draw in the level of public health risk for new license applications -- this whole slide is limited only to changes to be reported, but if you were to expand not only to the manufacturing changes to an approved license but actually include the requests for an application itself, it would be over here. It would be much higher.

So, basically, we have chose to insert this pilot to be implemented in the near future under

-- at a risk level where it's likely to be of sufficient interest because of its reasonable public health impact and not applications that one might consider trivial. However, we have chosen to stay out of the new license application area where we feel that the risk is definitely too much to be acceptable under a pilot program.

Just one more comment about the prior approval supplement, which is the category that contains the proposed two specific pilots. There's two types of prior approval supplements. You can categorize many things in many different ways, but for the purposes of this discussion I have chosen to categorize it this way.

There is a prior approval supplement that seeks to reduce the reporting level of a particular application request, and that request to report under a different category -- the request for an element that is pre-determined to be in the PAS category, a request to go from that category to something lower than that such as CBE-30 or CBE or even annual report -- such a request itself has to be approved up front as a prior approval supplement at least once but, if approved, that request will then allow you to report under a lower category.

This we have called the comparability protocol where the prior approval supplement proposes

to report the changes under a lower category than previously determined.

In addition to the comparability protocol, there is the more commonly understood PAS reporting category that's fixed -- that is, the reporting category as predetermined as a way of ensuring public health safety.

For those fixed reporting categories, we have those that have the pre-approval inspection as an element or those without that pre-approval inspection review element. So of the ones -- Of the fixed PAS reporting category with pre-approval inspection, I point out this is the exception, and this is the usual. We have two major exceptions, as you saw before, the irradiation and the red blood cell immunization program.

So pilots that we have selected are prior approval supplements with an inspection element which allows us to assess the impact of conducting the pilot, and again these are Gamma irradiation and red blood cell immunization programs, and I hope by now you have a good appreciation for the thought process that went into selecting these two areas as the pilot candidates.

So in terms of options for the applicant, if you are interested in supplementing your license to include Gamma irradiation for transfusion components

or the red blood cell immunization program for source components, you used to have just one option. You simply submit your submission to us, let us evaluate, let us do the inspection, and a decision will be forthcoming.

To that we propose to add an option, which is the self-certification to a CBER prescribed pilot guidance document or monograph, and that option represents the specific pilots.

Okay. Now we are 50 percent done. Basic concept number six: The two specific pilot guidances are currently being developed, and will be finalized under good guidance practice.

This speaks to the implementation date or the exact date of the pilot being effective. Under good guidance practice or GGP, it can either be three major steps or two steps, based on the level of public health risk.

What's shown in yellow here represents what would be, if it was a simple two-step process, but I'm afraid for the pilots we'll have to go through the entire process as it represents significant change and potential for public health risk.

The guidance has to be first developed and designated as being either level 1 or level 2, and has to receive internal clearance. That can then immediately move to the notice of availability of the

final guidance or it can go through notice of availability or NOA of the draft guidance in the Federal Register.

Following that notice will be a comment period during which the industry is invited to make comments. Those comments will be analyzed. The document will be accordingly revised, and we'll go through a repeat clearance process or some iterations between these two steps until the agency feels that there has been -- that the document is now ready for final guidance, at which time the notice NOA will be published in the Federal Register of the final guidance.

At that point of publication, the Federal Register will say exactly when the particular guidance will be effective. That's -- So look out for the notice in the Federal Register. It will tell you when exactly the pilot and the pilot guidance document will be effective.

So what we propose today here -- What we are describing today will not be effective until you see this notice, but the comments to this guidance are always welcome, even after its being effective.

Basic concept number seven: Once the pilot guidances have been finalized, once it has been finalized -- and finalized is the key word here -- alternatives or modified versions cannot be considered

as a specific supplemental application.

In other words, alternatives or modified versions is always welcome at the level of the guidance document itself. In terms of shaping or reshaping the guidance document, the comments are always welcome and will be considered. However, at the level of each specific application, once it has been finalized, alternatives or modified versions cannot be considered, and here is why.

In terms of guidance documents, the typical CBER guidance outlined GMP recommendations and, if firms have an alternative route that affords equivalent public health protection, the applicants are welcome to propose that alternative way of doing things, and it will be considered -- reviewed, considered and approved, if appropriate.

The guidance to be released under the Pilot program represent, so to speak, "pre-reviewed" licensing criteria which was intended to obviate the prior review of that supplement. So if you propose to deviate from that, there is no way for us to assess the impact of that until we review it; and once we review it, it defeats the purpose of the pilot program. So by definition, no modifications can be considered under the pilot program at the level of specific license application.

Basic concept number eight: Applications

under the pilot must be submitted as a variance request under Title 21 CFR Section 640.120, a variance request to the regulation 21 CFR 601.12(b)(3) which outlines the requirements for the PAS reporting category within the changes to be effected reporting requirement.

What does 601.12(b)(3) say? It basically states that the prior approval supplement shall contain detailed descriptions, protocols and data to support the proposed manufacturing change and an assessment of the effect of that change on public health risk, as well as some other requirements.

As a pilot, we are endeavoring to deviate from this regulatory requirement, which is sound, but in terms of moving forward with a pilot program to test a different way of doing things, we cannot apply the rule in its literal sense. We have to move to an exception.

As an exception -- To move forward with an exception, that puts us in the variance request category or a legal mechanism that allows us to deviate from the detailed regulatory requirement specifically outlined in 601.12(b)(3). So I hope that's clear as to why we have to use this regulatory mechanism.

Basic concept number nine: The evaluation criteria to determine the success or failure of the

pilots have not been rigorously defined. That's of necessity and by design.

How do we determine whether or not a pilot is a success? In trying to determine whether or not we have a reasonable database to make an evaluation, to begin with, we have to have some idea of how many number of applications that we have to process, and we have to have some idea of the timeline. These are difficult decisions to make.

We have arbitrarily chosen approximately one year for the timeline, but we have no idea exactly how many applications will be received during that time. We have no idea of the interest level from the public and the regulated industry to take advantage of the optional PAS reporting category, as outlined by each specific pilot.

We hope to use the findings at inspection, again the cornerstone of this pilot program, as defined today, to determine the number of applications and the actual timeline that should be. What we find at inspections in terms of uniformity of the level of adherence or conformance to the CBER prescribed documents or monographs and the public health implications of each of those findings will determine how many applications we have to ultimately assess and what the actual timeline will be.

So in a sense that you can view this

process that we're following as being somewhat analogous to the drug approval mechanism, which may not be all that familiar to this audience, but typically when a new drug is being developed, sponsors or companies will follow under a investigational protocol Phase I, Phase II, Phase III developmental processes.

Phase I is where you typically test out an idea, and one of the major goals of the Phase I is to define parameters by which you will conduct a more definitive or Phase III study.

We are following a kind of a similar concept. We have, by design and of necessity, not defined the actual parameters at this point, because we have little to base that kind of decision. We don't have enough information database.

This initial pilot -- Under this initial pilot we hope to gain that information on which we can base a more definitive pilot, and that leads into expanding the pilot -- the pilot program, I should say.

So at this stage -- At this initial phase of the Pilot program, the two specific pilots are being conducted with some idea of the long term goal under the Pilot program, but without specific concrete milestones to capture, and this is again where we need your input as well.

In terms of the immediate outcomes once you make an application, what can we expect? Well, we hope it to be an approval letter as soon as the inspection is scheduled and conducted within 90 days. But that may necessarily not be the case, in which case you will receive a complete review letter, as you already have, when you application is not approved at the first go-round. But that review letter will be -- will simply state whether or not -- Well, once that review letter is written, it will ask you to -- it will inform you that your application has withdrawn from the pilot, and it will explain the reasons why, and it's most likely going to specifically cite the inspectional findings as evidence of the fact that you have not been able to truly self-certify adherence according to the inspectional findings and, therefore, we are basically not considering your application under the pilot. But that is not to say that your pilot -- that your application cannot be considered.

Basically, once that review letter is written, then in your response back to us you have to apply conventionally. That is, you have to submit to us your operating procedure as you always have in obtaining approval for the changes that you propose.

Okay. So we are now at the last concept. We have -- In terms of expanding the Pilot, a plan to expand the Pilot program, currently loosely defined

based on the key idea of self-certification, to applications other than those covered by the two specific pilots has not been defined. This is where we need your input.

There has been some discussion within CBER as to how we might expand the pilot -- expand the Pilot program from these two initial pilot proposals, but those discussions are rather premature, because we have no experience gleaned yet from the two specific pilots.

We have some concrete ideas. However, we purposefully will not present them here, for the fear that you might misconstrue them as agency positions, and also to trigger you to independently think and propose to us, rather than simply parroting back on our initial proposals.

So the plan to expand the program, again of necessity and by design, has not been rigorously defined, and we would appreciate input on this.

So I have chosen the red background here to indicate to the audience that we are now at the concluding phase of this presentation, but after having done so, I realized that this list of ten basic concepts begin to look like the Ten Commandments. But I assure you, this is not the Ten Commandments.

These are simply basic concepts which is imminently modifiable, based on your input, and that's

the repeating theme of today's workshop that you've heard from speaker number one through -- that you will continue to hear until speaker number last.

The workshop is an interactive process. The whole idea of the Pilot program rests on the idea of self-certification. In fulfilling this goal we start out with two initial specific pilots under a broader Pilot program, and these two pilots represent optional PAS reporting categories as a new licensing mechanism.

The two specific pilots, which are elements of the options to the prior approval supplement reporting category, will support your supplement requests to the current ELA/PLA license, but in the future to the BLA, the biologics license or BL, I should say.

The whole specific pilot and the Pilot program itself will be implemented according to the guidelines established under good guidance practice, and this is specific guidelines that the agency has made public statements about in the past.

Once the pilot guidances or monographs have been finalized, modifications to that guidance cannot be considered at the individual application level, but can be considered at the overall program level.

The whole program has to proceed as a

variance request, because after all, the pilot is an exception to the usual way of doing things. Once we have gleaned sufficient information under the exception variance request route of conducting license reviews, then it behooves us to evaluate the impact, and we have to base our experience on this initial pilots that I have alluded to just a few minutes ago as being analogous to the Phase I stage of drug development. You might consider this being as the initial Phase I stage of a new policy development.

Based on that review experience gained under the specific Phase I stage, we will formulate a more concrete plan to expand the program so that it is of more use to you; in other words, in true streamlining effort to reduce the reporting burden, yet not compromise public health risk.

So we have allotted ample time today for panel discussions and question and answer sessions, and please write, if you don't speak today. There's various ways of doing that, but obviously, there wills be dockets under each specific pilot guidance. But in addition to that, please feel free to communicate more informally directly to the Blood and Plasma Branch, and you're welcome to direct your comments to attention my name.

That basically summarizes the ten basic concepts that I've tried to go over. I hope that sets

the stage for more in depth discussion of the two specific pilots for the Gamma irradiation as well as the red cell immunization program. Thank you.

(APPLAUSE)

MODERATOR CONLEY: Jong's allusion to the Ten Commandments struck me, because you'll remember that the first time Moses went up on the mountain to get the Ten Commandments, he came down and found that the people had turned away from the Word. That is not the goal of this process to find that everybody has taken absolute liberty and freedoms with the right way to do the process, and we will want to discuss some of that -- those risks, as we proceed further this afternoon.

Jong has given you enough of an outline that you understand where we are in the process now, that we are discussing very much at the front end a potential new approach. One guidance document is available as of yesterday, a second to be done in the not too distant future. Comment will be important.

This is not something you can go home and do now or even when the draft guidances are published, but when they are published as a final, then it's something you can take action on.

As you listened to or think about what Jong had to say, and as you listen to the additional presentations today, we would like for you to think

about the discussion questions that are in your package.

So if you would pull that gray sheet out and look at it with me now briefly, I would like to go over it, to put them in your mind and to start the thinking process, not to draw boxes around what you're considering but to start the process of what you're going to think about.

Now my slide tray should have a second set of slides that you can cue it to, please, and we'll keep the lights up since people are reading. Not too low, please.

First, is the concept of self-certification valid? You don't want to be too full of yourself and the work you do, but as Consumer Safety Officers at the FDA, I can tell you we often review SOPs that are in conflict with each other, that may be ill conceived, that may be lacking detail, that may have outright errors in them, that may not support the regulations or good manufacturing practices that are out there.

So I would like to pose the question to the audience to consider, has the FDA review of your SOP become a critical part of your QA process? If it has, is it something that you can, within your own organizations, provide adequate substitutes for an equivalent review or not?

Can we expect that the blood industry will conform to a published standard? In other words, are the products that blood bankers deal with routinely so inherently variable that it will be difficult or impossible to publish a single standard that the industry is willing to adhere to; or to put it another way, are the temperaments of those that are in control of blood banking such that adherence to a published monograph or standard is not a reasonable approach?

We want to ask this afternoon how many of you here today represent an applicant who would be interested in participating in one of these pilots, or how many of you are aware of colleagues that you think would be interested in participating in one of these pilots, because again we have to prove that the system works before we can move ahead.

The future may be to have many or possibly all of the routine blood products through a monograph review. Clearly, we won't have the staff to always have a pre-license inspection be a component of that. So part of what we're trying to prove through the pilot and the pre-license inspection is that it is a system that can stand on its own. I think it's a real question I'll really be interested in your input today.

The next two questions are really companion questions, because they're about the two

particular pilots that we're talking about today, both irradiation technology and the red blood cell immunization approach.

The question really is technical in nature. Are the proposed guideline for one that you have in your handouts today or discussion about a guideline -- are they technically sound and scientifically sound and accurate to that point?

A lot of these kinds of comments will require supporting documentation about why you think that the technical issues should be addressed in a different way. You may not have that at your fingertips today. We certainly want to hear your comments, and again with the opportunity to respond in writing, then you can provide supporting documentation, scientific evidence why you might disagree with the outline.

Further, we have to decide what criteria we're going to use to evaluate this self-certification pilot. While we've discussed a lot internally, it's clear, as Jong said, that this is a new experience.

So how many participants should be a baseline before we would call the program a success or not? Three? Six? Ten? Twelve? Being that both of these approaches have been around for a while, it may be difficult to get large numbers, but it's important that we prove that the system works.

What objective evaluation criteria should be used to judge an individual self-certification applicant as either being successful or not under the self-certification program?

Obviously, one standard could be no 480 cites on the inspection. I'm not sure if that's reasonable or not. Should we say only minor 483 citations? What would constitute a minor citation? Again, we're in an arena that is new enough to us that we would really like the input from the industry.

If the concept of self-certification against a published standard proves to be sound, what products or processes should next be included in the program? We've started with two here in the pilot. If the approach proves sound, you heard Dr. Epstein say this morning that we're posed to move as quickly as possible forward in applying it to additional products to streamline.

Finally, what is the best way to involve the industry in future developments? There have been things that have been tried in the past. We've worked with the Coalition for Regulatory Reform. Perhaps that would be the group to work with again in developing new guidance documents or new monographs, but again, frankly, that's not totally clear to us.

We would like to hear from you, the industry, the manufacturers, do you feel that the

Coalition, the CFRR, is an adequate representation or representative for your needs and desires and things that are important to you, or would you prefer that the FDA assemble its own panel of representatives from licensed applicants. If so, how should that panel be assembled? Do you have a concept of how future guidance documents or monographs should be produced?

Even if you identify an agency representative that you think should work on these, do you prefer that FDA do the first draft and then come to them, or would you prefer that industry do a first draft and then come to FDA?

We're blazing new trails. Lots of options are open to us. The kinds of things that I've asked you to think about here should not draw boxes around what you're going to think about, but instead to just open up the area for discussion. So please think about those. This afternoon it's going to be your show, and hopefully, have some good give and take.

I'll remind you that there are cards in your folders where you can write down your questions, legibly and carefully considered. You're welcome to give them to me or to people at the front desk, and after lunch we will have people circulating in a room to collect those.

When we reach our discussion time, we will first try to answer the questions through our panel,

and then we will, after a break, invite open discussion on the issues. So, hopefully, you're ready.

Our next presenter is Mary Ann Denham. Mary Ann is a Consumer Safety Officer in the Division of Blood Applications. She joined the FDA in 1991. Prior to joining the FDA, she worked in a variety of administrative and technical positions in blood banking. She's a Registered Med. Tech. and a blood bank specialist.

She received her B.S. degree in medical technology from the University of Kentucky, and is a strong supporter of University of Kentucky athletic teams. She also has a certification in clinical immunohematology from the University of Tennessee and an MBA from Jacksonville University.

Mary Ann will present the information included in the most recent draft guidance document that you received this morning on the irradiation or blood products.

MS. DENHAM: Okay. Well, trust me. Just because the weather this past week was like Florida, you can get in the mood for Christmas. So this is where I'd rather be, on the beach.

I wanted to tease Mary. Since I have a degree from the University of Tennessee and the University of Kentucky, I'm rooting for the University

of Kentucky.

Today we're going to talk about Gamma Irradiation, and you got the draft document that was published yesterday afternoon. So I'm going to go over the points of the document.

As you know, I'm Mary Ann Denham. I'm a Consumer Safety Officer, and I'm giving you my phone number, my FAX number.

As you know, the reason why we irradiate blood and blood components is to prevent graft versus host disease. The reason why is the gamma radiation decreases the number of viable T lymphocytes. This occurs when viable T lymphocytes in the blood and blood components engraft, multiply and react against the tissues of the recipient.

Those patients that are at risk are those that are immunocompromised. Although there is some controversy over which immunocompromised recipients are at risk, that should be decided by the hospital transfusion service or the -- I should say hospital transfusion committee or the medical review board.

The other at risk group are non-immunocompromised recipients who receive blood from family members. I'm not going to go into all the details, but there is some background in your document and, of course, there's a lot in the literature.

The blood and blood components that have

been implicated in graft versus host disease are primarily those that contain lymphocytes and have been reported in the literature. These are platelets, platelets pheresis, granulocyte pheresis, whole blood, red blood cells.

Then the question comes up, well, how come you licensed other components for irradiation? Well, when it came right down to it, we licensed those that requested irradiation. So that's the reason for that. Those products are primarily ones who contain either no lymphocytes or few lymphocytes and are not generally reported in the literature.

Now there's several methods of reducing leukocytes, washing, filtration, centrifugation. I've put a little note here under filtration. Since we're probably going to do wholesale leuko reduction in the near future, it's important to remember that leuko reduction does not eliminate the risk of graft versus host disease. So even though we are doing leuko reduction, it's still important to do irradiation on those products as well.

Of course, the only method that's known for inactivation of leukocytes is the gamma irradiation.

Okay. Now I want to make -- It's important to make clear that this is a proposed pilot, and this is our current thinking. So we do appreciate

comments.

Irradiation performed by an applicant establishment: They should follow the GMP regulations in 21 CFR 606.210 and 211, and they should have an unsuspended or unrevoked license.

I wanted to mention training here, even though we didn't put it in the document, that training is part of GMPs. It's important that the people using the equipment for irradiation should be trained properly using the operator's manual.

They should know the risks of irradiation. They should be told what measures should be taken for irradiation safety, so that the anxiety and the fear of doing irradiation should be eliminated, and they should have annual retraining.

SOPs should be developed, approved, implemented, and maintained in the following areas, and we're going to discuss those, and I've given you the CFR cites.

The comment came up, who approves it. It should be an internal approval process, either by the authorized personnel or the QA, whoever in your facility is authorized to do that.

For the purposes of the pilot, we had to eliminate some variables to see if the pilot would be effective, and one of the areas we did this in was in the 510k cleared blood irradiators. In other words,

you have to be using a 510k cleared irradiator.

The next slide tells you the companies that have been cleared by the FDA to do blood irradiation. The reason we didn't include the linear accelerators is because the use of linear accelerators for irradiation of blood components is an off-labeled use, and that presents a lot of other variables in trying to regulate this area. However, if you want to use a linear accelerator, you can still apply under the regular PAS procedure.

Okay. So your equipment, of course, should have manufacturer's instructions. All equipment should be qualified for use, and the equipment should be calibrated.

Now then the next question comes up, what is the dosage and the time to deliver the dose? Well, in our previous memo we have used the 2500 Centigrade targeted to the central portion of the container and the minimum dose of 1500 Centigrade at any other point. So that's FDA's policy regarding the dose.

The time required to deliver the dose should be based on the irradiation intensity of the dose. Now each piece of equipment should be provided by the -- when you get your equipment, the manufacturer should provide a written calibration of the dose, the central test dose, and this calibration certificate specifies what the dose started out or the

intensity of the source started out -- I'm sorry.

The equipment that we've discussed before comes with either cesium 137 or cobalt 60. Now the intensity of the source -- the dose will vary over a period of time based on the decay of the dose -- I'm sorry, the decay of the source. So the source is constantly decaying. So the irradiation time must be adjusted periodically over the life of the source.

The manufacturer will provide a decay table, and the time must be calculated on the central dose rate that they've already provided and the decaying factor.

The maximum number of units to be irradiated at one time should be based on the manufacturer's instruction, and usually depends on the size of the canister.

The total irradiation dose should not exceed 5000 Centigrade to any portion of the container, and this we allowed because, if your indicator did not work, this gave you an opportunity to irradiate one more time.

Under the pilot another variable we eliminated is, if you want to use 3000 or another figure other than the 2500, that's not -- our proposal is not to allow that under the pilot program.

The next point is the indicators. The FDA's recommendation for irradiation has always been

that each batch should have at least one indicator. This -- We have had several controversies over this, but that's our policy.

If you want to put an irradiator -- I mean an indicator on each product that you're irradiating, that's perfectly okay. Now there's several on the market. Most of them are based on X-ray film, and it's important that the indicator be stored in the proper conditions according to the manufacturer's directions; because if you're using something like X-ray film, if it's not in a dark area, then that changes the color or darkens it, as a rule.

You need to verify that the indicator has not been exposed to unacceptable temperatures. Some of these come with a little temperature card that changes the color with a dot. You should have an explanation of the expected results for each new lot. We recommend that you compare it with the old lot. In other words, just irradiate both the new lot and the old lot.

Your SOP should have corrective action, if the indicator doesn't work and, of course, this should always be documented.

Labeling: Permanently -- The product should be permanently labeled as irradiated on the product label. Even in the pilot as in the regular PAS, labels have to be submitted to CBER for review

and approval. Only FDA approved product codes and names should be used.

It's important to point out here that the indicator is not a label. I see that in SOPs and everything, but it is not a label. It's an indicator. That's the only purpose. The purpose of the indicator is to say you turned the machine on, and it operated.

The little purple attribute label that was put up in the lefthand corner in the original labeling requirements is no longer applicable, and there should be no tie-tags.

Okay. Now we're going to talk about the dating period for the products. As you probably know, the red blood cell products are the ones most affected by the irradiation. So based on scientific data, the 28 days from the date of irradiation is the dating period on red cell products, or that should not exceed the original expiration date.

There's no information regarding adverse reactions for the platelets and plasma products from the irradiation. So that should not be changed. So it should be the same date.

Okay. Now let's talk about quality assurance. There's two points to the quality assurance, process validation and the quality control. When we're talking about validation for irradiation, it means measuring the amount of irradiation absorbed

by the product, including a load configuration using pre-determined parameters.

In other words, you need to follow the manufacturer's directions of how the machine should be packed and so forth. It should be performed on a fully loaded canister, whatever the manufacturer recommends, and it should be performed using a dosimetry system.

Now your dosimetry system should generate a dose map, using the dosage that is going to be used. If you're going to use 2500 Centigrade, don't do your dose map at 3,000. You'd be surprised at the number of submissions that come in that way. So 2500 Centigrade should be what your dose map should use -- be set for.

The dose map is used to evaluate the relative dose, not to adjust the time of the components. The dose map should be done when the machine is put into service and annually for cesium 137 machines and semi-annually for cobalt 60 machines and, of course, after major repairs.

The dose map is the dose distribution. The dosimeters are used to map the dose distribution in the canister. This is examined to determine if there are areas where there's not going to be a 1500 Centigrade level.

Usually this happens at the top of the

canister, at the bottom of the canister. A lot of people who have lower dosage at the bottom use a spacer. Most of those are usually styrofoam. If it's at the top, then they avoid packing at the top.

These dose maps are done using a phantom or a blood bag that has TLD chips. There are any number of ways to do that. The medium for dosimetry should closely resemble blood, and in the literature you have water. The acrylic is used. So whatever would -- is in the literature that would be recommended, but I think most people are using the water or the plastic.

Okay. In using your -- In starting up your machine or putting your machine into service, you should run three test runs. That means, in other words, you pack the canister like you plan to use it all the time, and run three procedures. You do this when you put it in service and, of course, after major repairs. It's important for QA to review these procedures.

Now quality control: Equipment: Quality control is performed on a scheduled basis. Usually this is determined by the manufacturer. Each date of use, the timer should be checked, and there should be a visual check at the turntable.

One of the areas where there have been a lot of problems is with the turntable. Some of the

machines have a window that you can check it through. Some of them have a period before you have to shut the door that you can see that the turntable is moving.

Your timer should be checked monthly against the National Institute of Standards and Technology's timer. This can be done by phone. They have it on a telephone that you can just call up and get the thing and just check your timer, or you can have a NIST certified timer.

The next area is periodically to do a leakage. This is to determine if you have leakage from your machine. These machines are really very safe. They have a credible amount of lead in them to prevent any leakage, but it is important to check this.

There are two ways this can be done. One is using a Geiger counter. The other is using a wet wipe and then counting the wipe.

We have not recommended employee badges, primarily because that's the purview of the Nuclear Regulatory Commission or the state who is responsible for radioactive material. However, if you do use employee badges, the current legal dose is 100 millirams per week. I have also seen badges on the machine to check leakage. So --

Of course, record keeping: There should be documentation of the significant steps in the

process, the duration of the irradiation process and, of course, it's important that your products not be out of the storage temperature for longer than 30 minutes.

The dose for each batch should be recorded, the identity of the person performing the irradiation, the date, time and site of the irradiation, if you're not the one -- if it's not being done at your facility.

Now in the pilot we did recommend that the irradiation could be performed by a contractor, as long as they were using the 510k cleared machines. So again here you have to have standard operating procedures so that the contractor knows what he's supposed to do, and you know what you're supposed to do.

The contractor should know that he has to register, and there are legal responsibilities. There should be a written agreement stating what they're doing and what you're doing, so that everybody is on the same wave length.

It should be noted here on the inspection, when the pre-license inspection is performed, the contractor will also be inspected. If in the future a contractor is added or changed, then a PAS supplement will have to be submitted.

Okay. We're back on the beach. If

anybody has any specific comments or questions about, you know, the specifics of the irradiation, I'll be glad to answer those. No? Back in the back?

MS. GALSKY: (QUESTION FROM THE AUDIENCE)

MS. DENHAM: As long as it's in the SOP, we don't have any -- We don't say they can't.

MS. GALSKY: I know.

MS. DENHAM: Most of them don't want to. At least that's been my understanding when I've inspected. They don't want to label the product.

MS. GALSKY: In our case it's only a transfusion service.

MS. DENHAM: I'm sorry?

MS. GALSKY: It's an associated transfusion service. It's under the same parent. It would be okay?

MS. DENHAM: Sure. It would be okay for them to do that, as long as it's in the SOP and everybody understands who's labeling and how. I think there's some feeling that, if they're -- The contractor should read the indicator. You know, they would have to be knowledgeable about the indicator so that they would know if the irradiation was performed properly.

So then they could put the label on.

MS. GALSKY: Okay, thanks.

MS. LeBEAU-LAIRD: Hi. Will the pilot

include both facilities that have their own irradiator as well as facilities that send their irradiation to another facility?

MS. DENHAM: Well, they would be the contractor. The other facility would be the contractor.

MS. LeBEAU-LAIRD: Okay. But I mean, that would be included in the pilot?

MS. DENHAM: That would be included in the inspection, yes.

MS. LeBEAU-LAIRD: No, no. In the pilot?

MS. DENHAM: Yes. Both the contractor and the other facility would be included. Okay? Did I answer your question? Okay. Anybody else?

MODERATOR CONLEY: Before you run off, just a comment on contract issues; because under -- As we become more like the rest of FDA in the regulatory process, we expect to see more contracting by licensed manufacturers.

Just remember that the product bears your license number, and you are responsible for the product. So as long as you have coordinated SOPs and have appropriate QA oversight over your contractor, there's no problem having a contractor do manufacturing functions, including labeling, on your behalf. Just make sure it's under control, and it's included in your QA oversight.

We're doing very well on time. I'll remind you that you have cards for questions. Especially if you've got anything that's really going to stump us, it would be nice if you turned it in before lunch so we can argue -- discuss it over our own lunch.

Other than that, we will break now. We will return promptly at 12:30 and begin again. You've got a nice lunch break. Enjoy your time in Rockville.

(Whereupon, the foregoing matter went off the record at 11:29 a.m.)

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

(12:40 p.m.)

MODERATOR CONLEY: Did everyone have a good lunch? The one thing I'm amazed about, since I came to FDA, are the number of restaurants that you can find up and down Rockville Pike in this neighborhood. You can usually find something you like.

A couple of additional reminders and asides. Out on the table this morning when you came in was the announcement of the availability of the ISBT labeling documents through the FDA. Just a reminder that you -- that's there to remind you that it's available, and it's something that we should all be looking toward, using that standardized labeling.

Also in your package are evaluation forms. I mention that now in case somebody does have to leave before the end of the meeting. How often do you get to evaluate the FDA? We would appreciate it if you would take time to fill that out about the usefulness of the workshop and the opportunity to comment on future initiatives.

I'll remind you again that you have cards in your folders or, if you've already used up your three cards, you can certainly borrow one from your neighbor or write it on a scrap paper. We have a nice stack of cards to start off our conversations this

afternoon, but we would appreciate more.

Our next speaker is Elizabeth Callaghan. Elizabeth is a Consumer Safety Officer in the Division of Blood Applications in CBER. She is presently detailed to the Office of the Director to work on the blood action plan and the rewrite of the requirements in the Code of Federal Regulations for blood and blood components.

She also provides guidance to the regulated industry, trade associations, consultants, consumers, FDA investigators, FDA district offices and other centers in FDA.

Elizabeth received her B.S. in Med Tech from the State University of New York at Stonybrook and her M.S. in biology from St. Johns in New York. She also has her SBB certification.

She will present the information included in the most recent internal draft of our proposed guidance document for the use of red blood cells for the immunization of plasma donors. Elizabeth.

MS. CALLAGHAN: Welcome back, now that you can all go to sleep and not pay too much attention to me.

Can I just do the first slide? The second pilot program that FDA is proposing is for the immunization of source plasma donors using immunogen red blood cells obtained from a licensed supplier.

After Gil's glowing introduction, this is sort of redundant, but Mary Ann insists I keep it in here for consistency. I would also like to take this time to thank Mary Ann for making up all these slides while I was in Florida on vacation.

The first section I would like to cover concerning the red blood cell immunization program is applicability. In order to participate in the pilot, the source plasma manufacturer must hold an unsuspended, unrevoked license for the manufacture of source plasma.

The purpose for participating in the pilot program is that the source plasma manufacturer seeks to supplement his or her license to include a red blood cell immunization program.

To participate in the pilot program, the source plasma manufacturer must obtain the immunogen red blood cells already thawed and deglycerolized from an approved manufacturer per a written agreement. The written agreement will be reviewed at the time of inspection.

The supplier of the immunogen red blood cells must hold an unsuspended, unrevoked license, and the supplier must be approved for the preparation of the immunogen red blood cells.

In order to apply to participate in the pilot program, the applicant must submit a completed

FDA Form 356h. Although this form is not approved yet for the use by blood and plasma establishments, it will be by the time these pilot programs go into effect, a self-certification statement that indicates the manufacturer's compliance with all applicable FDA regulations and conformance with the specific licensing criteria for the immunization of source plasma donors with red blood cells, proposed labels to be used on the product, and a request for a variance under 21 CFR 640.120 to the provisions of 21 CFR 601.12(b)(3) which requires detailed submissions including SOPs and validation data.

At the time you submit the documents to FDA, you should be ready for inspection and have at least five donors participating in your red blood cell immunization program. In order to be considered for licensure under the pilot program, the source plasma manufacturer must have the following requirements in place: medical oversight and quality assurance; standard operating procedures which pertain specifically to the immunization program; manufacturing records and a final product labeling; and records including monitoring of the immunization red blood cell supplier.

Let's discuss these requirements one by one. First, medical oversight and QA: The applicant must be able to demonstrate that the red blood cell

immunization program is under the direction and supervision of a qualified licensed physician.

By qualified, we mean that the physician in charge of the program at the location seeking licensure must have a thorough understanding of what the program is about, what problems the donor may encounter and how to deal with them, why donor antibody titers are reviewed and their relation to whether immunization red blood cells should or shouldn't be given, and the physician must be able to clearly convey this information to the potential participants in the program.

Inspectional observations have found that this is where most programs are lacking. The physician in charge of the program does not seem to have a total comprehension of what he should be doing.

In addition, the applicant must demonstrate that their quality assurance program includes oversight of the red blood cell immunization program.

Second, let's discuss the SOPs. The source plasma manufacturer must develop and maintain standard operating procedures to control all relevant, specific aspects related to the immunization program. And to sound like a typical FDA person, these should include but are not limited to the receipt and storage of immunization red blood cells from a licensed

supplier, the procedures for donor-cell matching and for scheduling of immunization injections, the procedures for preparing the immunization red blood cells for injection, the procedures for obtaining the informed consent from the donor, the procedures for actually immunizing the donors using the red blood cells and for monitoring the donors, both for adverse reactions after the red cell injections and for the production of antibodies.

Okay. Now let's discuss some of the specifics of the SOP requirements. The SOP for receipt and storage of the immunization red blood cells should include: The immunization red blood cells must be evaluated upon receipt from the supplier in order to verify that the proper shipping temperature of 1-10C have been maintained and the labeling accurately reflects the product.

The label and any accompanying documentation should include the product name, ABO and Rh, the volume of the product, and identifying information which allows tracing back to the original donor and to all the procedures involved in the manufacture of the product.

The product label should also include the storage temperature, the expiration date, a cautionary statement for RBC immunization only, the name, address and registration number of the supplier, and the label

should not cover the entire vial to permit visual examination of the contents.

The immunization red blood cells should be stored between 1 and 6 degrees Centigrade, in order to help assure product sterility and the integrity of the red blood cell antigens.

The SOPs for donor cell matching and planning of the immunization schedule should indicate that a medical director selects the donors to participate in the immunization program, based in part on the knowledge that future pregnancy is not possible, whether the donor has preexisting alloantibodies, and the potential for developing new alloantibodies, any previous history of donor exposure to the red blood cell immunizations.

The exposure of the donors for immunization red blood cells should be minimized as much as possible in order to minimize the risks of developing unwanted alloantibodies, and the possible exposure to infectious disease agents, and a specific exclusion criteria for participation in the program. I'll discuss these in a little while.

A donor record file must be established and maintained for each donor participating in the program. The source plasma donors must meet all normal donor suitability requirements.

Now back to the inclusion and exclusion

criteria. The inclusion and exclusion criteria should indicate that a qualified, licensed physician responsible for the selection of donors, including ensure future pregnancy is not possible, the matching of the immunization red blood cells according to the donor's antigen cell type, review for any preexisting alloantibodies, and the development of additional alloantibodies, and a plan to evaluate each donor's specific immunization schedule based on the donor's response to the immunization and any prior history of immunizations to decide whether the donor should continue in the program.

Additional requirements for participation in an immunization program include: donors who have not been previously immunized with red blood cells, de novo donors, as we call them, may participate in the program, but should only be immunized against D.

Immunization with other red blood cell antigens should be limited to donors with corresponding, preexisting alloantibodies.

Both the immunization red blood cells and the source plasma donors must be tested at a minimum for ABO and an Rh antigen profile, including D, C, c, E, e, as well as K, Fy(a), FY(b), Jk(a), and Jk(b).

Selection of the immunogen red blood cells for a specific source plasma donor should include appropriate phenotypic matching in order to elicit a

rise in the antibody only -- a rise in only the desired antibody, limiting the donor's exposure to as few immunization red blood cell donors as possible.

Assessing the immunogenicity of the immunizing cells, evaluating the immunological response of the source plasma donors in general, screening for alloantibodies and identification of the antibodies, if any are detected, the immunization schedule should be established prior to the first injection and continuously monitored for response after each immunization.

The immunization schedule for de novo donors should be limited to no more than 4ml per injection, five injections a month, and a limit of ten injections in a six-month period. Oh, yes, it is on the slide. It's not on the next one. Donors who do not respond after receiving a total of 150ml of immunogen red blood cells should be dropped from the program.

Donors with preexisting alloantibodies should be immunized with an antigen that corresponds to their preexisting alloantibody, and the immunizations should be limited to no more than 4ml of red blood cells per injection, no more than five injections a month, and a limit of ten injections in a six-month period and -- unfortunately, this didn't come out on the slide -- not to exceed a total of

150ml per year.

The immunization schedule must indicate the information pertaining to the immunization red blood cells, including lot number and any other pertinent information found on the vial, volume to be administered at each injection and the site of injection, the interval for booster immunizations and the criteria for discontinuing a source plasma donor in the program.

The criteria for discontinuing a donor in the immunization program include: Voluntary withdrawal on the part of the donor; if a donor experiences severe adverse reactions; if the donor elicits no response or an inadequate response after being immunized with red blood cells of 150ml.

Let's move on to processing the immunization red blood cells in preparation for administering to the donor.

The thawed deglycerolized immunization red blood cells should be stored between 1 and 6 degrees Centigrade for a period not to exceed the expiration date on the product label.

Prior to the release for injection the immunization red blood cell product should be examined to detect abnormalities, including hemolysis, discoloration and microbial growth. If the immunization red blood cells are not used within four

hours after being removed from the storage vial, they should be destroyed.

All donors participating in the immunization program must sign an informed consent specific for the red blood cell immunization program. The informed consent must be obtained after a qualified, licensed physician has explained the immunization program and the hazards involved, including the risks of a hemolytic transfusion reaction, the possible exposure to infectious disease agents.

The explanation must be given in a manner that allows the donor to make an intelligent, informed and voluntary decision to participate in the program and should also include the expected rate of success, the volume of the red blood cells to be injected, the route of administration, the need for booster immunizations, the criteria for discontinuation in the program, a statement that the donor has had an opportunity to ask questions, a statement to inform the donors they may participate in only one immunization program at a time, and a statement to advise the donors that they may withdraw from the program for any reason at anytime.

In addition, the donor should be informed that testing for antibody detection and identification should continue for a minimum of 12 months after the

last immunization, even if the donor has withdrawn from the program, of possible adverse reactions and that they must be incapable of becoming pregnant, of problems which may arise if blood transfusions are needed in the future and the potential for infectious disease transmission.

On to the actual immunization and monitoring of the donors who are receiving the immunization red blood cells. The injection of the immunization red blood cells must be performed by a qualified, licensed physician or a person under the physician's direction and control who is trained for such procedures. However, the qualified licensed physician must be on the premises when the red blood cell immunizations are being given. There are no qualifications other than that.

Immunization recipients should be observed for at least 15 minutes following the injections. A qualified, licensed physician must assess the donor's response to the immunization red blood cell injections, determine if the donor is eligible to continue in the program and evaluate any adverse reactions.

Additional donor monitoring should include a review of the pre-immunization antibody titer, any post-immunization antibody titer results, antibody detection and identification panels, and the

cumulative immunization red blood cell exposure, and any adverse reactions to receiving the immunization red blood cells.

A source plasma donor should be monitored for a minimum period of 12 months from the last immunization red blood cell injection for potential infectious disease transmission and for the development of alloantibodies.

Any unexpected findings should be investigated and reported to the supplier of the immunogen red blood cells, and be documented in the donor record file.

Manufacturing records and final product labeling: The source plasma label must indicate that the product has been collected from an immunized donor as well as indicate the antibody specificity.

The performance of each step in the manufacturing of the source plasma must be documented as part of a permanent product record, and records must include the immunization red blood cells used and the disposition of the source plasma. All donor specific information must be documented in the donor record file.

Last but not least is the applicant's monitoring of the immunization red blood cell supplier. The applicant must assure that the immunization red blood cell supplier manufactures the

cells according to the standards established in the CFR and in compliance with current good manufacturing practices.

The applicant should perform a periodic review and an audit of all records relevant to the supplier's manufacturing of the immunization red blood cells, verify that the supplier performs all appropriate look-back investigations, product withdrawals and any other product related notifications thoroughly and a timely manner, assurance that the immunization red blood cell donors meet all donor suitability requirements and that all manufacturing procedures, including cell cryopreservation, deglycerolization and aliquoting comply with current good GMP.

Hopefully, when this pilot program is finalized, your desk will look a little less like the one in the foreground and a little more like the one in the background, so that instead of filing SOPs with the FDA, you can be doing more exciting things like reviewing Internet IPOs.

(APPLAUSE)

MODERATOR CONLEY: I'm beginning to sound like a bit of a nudge, but I'll remind you there are cards in your folders. At the close of the next talk, we will have people circulating in the room to pick up those questions, because we'll move right into the

question and answer session.

So if you have any questions regarding the immunogen red blood cell future guidance document and our thoughts on that or, as the next speaker discusses, the licensing issues behind this pilot, by all means, jot them down and we will answer them first in our question and answer session.

Our next speaker is Dr. Leslie Holness. Les is a medical officer in the Division of Blood Applications. Dr. Holness received his B.A. from New York University and his M.D. from the Faculty of Medicine in Bucharest, Rumania.

He joined CBER after pathology training and practice at Harlem Hospital in New York, and I think he misses New York daily. He loves the place. He also did a fellowship in transfusion medicine at the New York Blood Center.

Dr. Holness has been with CBER for seven years. He's worked on policy revision for donor suitability, health hazard evaluations, and review of investigational new drug submissions, IND submissions. He also manages our FAX inquiry system for rapid response on current policy.

Dr. Holness will discuss the application process, how it will work under the proposed pilot program.

DR. HOLNESS: Thanks, Gil. It looks like

I have the other half of your tie.

As Gil mentioned, I'm Les Holness to talk about the implication of self-certification. As John mentioned this morning, the program is a variance under 21 CFR 641.20, and I will try to explain the application process for the pilot.

As you heard, the pilot is a proposal for manufacturers to self-certify conformance to specific criteria set out in the guidance. There are some good things about the program.

There's no CBER review of submitted information, as is normally done in the BLA or PLA supplement filing. There's no SOP submission, and there's no data to be submitted derived from validation or QC testing.

Because of the significant risk to public health, both programs are prior approval supplements. The products may be manufactured but not distributed interstate until the supplement is approved.

A draft version of the document reviewed by Mary Ann is available to workshop participants, and the document that Liz reviewed will be published according to the following sequence of events.

There will be a notice of availability of the documents published in the Federal Register. There will be a 90-day comment period, after which the final document will be published.

As Liz mentioned, the prerequisite for the program is an unrevoked, unsuspended license for the parent products. This means for irradiation, you must be licensed for the products you're irradiating -- for example, red blood cells, whole blood, platelets, etcetera. For the red blood immunization program, you should be licensed for source plasma.

Now on to the submission. Submission includes a request to the Director of CBER for an exception to filing a supplement to your product license under 21 CFR 641.20; secondly, a self-certification statement certifying that the manufacturer is in compliance with all the FDA regulations and meets criteria set forth in the applicable document.

Application Form FDA 356h, which Liz mentioned, is not in use at the moment for blood and blood products, but will be by the time the program pilot is implemented.

Labels should also be submitted. Receipt of the documents will indicate readiness for inspection. The FDA will review the documents, schedule and conduct the pre-license inspection within 90 days.

This slide is for label submission. Labels should accompany one form of the FDA 2567, two copies of each label, and a copy of the circular of

information, if applicable.

This is the address for the application form, and it's in your handout. Gil insists that I include a cartoon in my presentation, and the caption says, "It won't be easy to get everyone to wear that all the time."

The inspection will be conducted by CBER, together with the District, and it will include the firm and appropriate contractors. This will be a comprehensive and in depth inspection, and will take longer than the routine pre-license inspection for supplement approval. It will not save the FDA any resources.

The inspection will concentrate on the process and the SOP, and will verify conformance with the guidance documents with respect to missing requirements in the document, etcetera.

The inspectors will be looking for deficiencies of quality assurance that may affect product safety, purity and potency. Compliance with all good, current manufacturing processes will be reviewed, and a 483 will be issued, if warranted.

Most manufacturers that have not complied with the guidance will be asked to submit a complete BLA supplement with appropriate documentation.

After approximately one year, depending on the number of participants, the FDA will evaluate the

program and make the evaluation available to the public. As the FDA has an ongoing commitment to streamlining the licensure process, if the program is effective and efficient, it will be extended to other blood products.

Once a notice of availability is published in the Federal Register, the document can be obtained at this address in your handout. Just send them a self-addressed adhesive label. They will send you a copy of the document.

These are the numbers in your handout for the CBER voice information system and the CBER FAX information system. Document number 9999 is a complete list of documents. Document number 9998 are documents added in the last 30 days.

If you're on the information superhighway, there's a complete list of documents by bounce-back E-mail at the address in the handout. For specific documents there's an E-mail address with document name. For questions and comments about biologics, the Office of Communications and Manufacturer's Assistance, OCTMA, has the last E-mail address in the handout.

That concludes my comments for today.

(APPLAUSE)

MODERATOR CONLEY: I'll ask those who were speakers today, please come forward and join us here

at the tables. Joe, could you be sure someone circulates in the room now to pick up any questions that people have.

While people are coming forward, it's a good time to say thank you to the speakers today, and also to the planning committee for this workshop, the people who were listed in the flier that was distributed announcing the workshop. That included Dr. Lee as Chairperson, Judy Ciaraldi, myself, Mary Ann Denham, Dr. Holness, Joanne Pryzbylik, and Ken Zemann, although in fact, being a small group within our branch, we pretty much all do everything together, and everybody in the branch is to be thanked.

We should also thank Daria Reed who works in our office and punched up a bunch of our slides with some color and a little bit more organization, and also thanks to Joe who is bringing me more questions. He's like the de facto member of every presentation effort that comes out of the Office of Blood.

Also, thanks to all of you for writing clearly, at least in the cards that I read at lunchtime, and the second batch will be the surprise questions. Since we've seen these others, we'll start with them.

We're doing very well on schedule, and when we finish all the questions and answers, I will

be asking you all to participate, and we'll also make a group decision as to whether we want to skip the afternoon break and plow on through and maybe go home a little bit early. But let's see how the time goes.

First is a question for Mary Ann. If a licensed facility has previously submitted a package on irradiation, will the facility convert to the pilot program or will you allow the package to rest with CBER?

MS. DENHAM: Well, considering how long it would take for the pilot thing to go through, we probably -- it would be better off to leave it where it is, but we would not automatically change it to the pilot program. No.

MODERATOR CONLEY: Can you all hear adequately? Okay, good.

Also for Mary Ann: Can I participate in a pilot study for irradiation if irradiation will be performed by an already licensed facility? Will that facility have to be reinspected?

MS. DENHAM: The answer is, yes, you can. We discussed the fact of whether the licensed facility would have to be inspected again. There will probably at the discretion of the inspector, and it would depend on when the licensed facility was last inspected and if irradiation was covered on that inspection.

So it would be primary discretion of the inspector.

MODERATOR CONLEY: With each of these questions, I'll try to look out in the audience. So if it was your question that's not been fully answered for you, raise your hand and come to one of the microphones, and we'll get clarification.

For Mary Gustafson, two questions on this card: First, what is your plan if a sufficient number of pilot submissions are not received?

CAPTAIN GUSTAFSON: Well, first of all, the notice of availability for the first pilot will have not only a request that you make comments on the guidance document that would be used to standardize the pilot, but also to see if there's any interest in the pilot.

If there is no interest in one or both of these pilots, we won't give up the project. We will try to substitute with another pilot area, and that's where, you know, we would really like your input into what are some of the areas that you would be interested in.

Unlike other drug development initiatives where you have an investigational phase and you can look at your IND workload to try to determine what your licensing workload is going to look like, we don't have that in the blood component area.

We, you know, can sometimes glean what's kind of coming down the pike from our discussions with industry, from published articles, and I'd say maybe the transfusion area is a little bit more predictable.

In the plasma area, we never really can foresee what changes are going to be happening in the future. So we really do need your input to see whether we've selected two pilot areas that we will have adequate participation or whether, you know, maybe we should forego one of them and go to another area. But we don't plan on giving the whole thing up unless there's absolutely no interest from anyone in any type of self-certification licensing.

MODERATOR CONLEY: Second question for Mary on the same card -- really, a series of questions: Must pre-license inspection be a component of any pilot? Could evaluation of the product be substituted -- for example, platelets? Could examination of QC data for product be used in place of pre-license inspection and evaluation of the product by FDA?

CAPTAIN GUSTAFSON: For the two areas that we have selected, the pre-license inspection would be an integral part of it. That's how we're going to evaluate whether the self-certification is adequate.

As Dr. Lee mentioned, these are areas where we now have pre-approval inspections as a part

of the approval process for these supplements.

For future pilots, I think we are amenable to any suggestions from you. It doesn't necessarily hold that the pre-license inspection has to be built into the self-certification. There could be other ways of evaluating pre-approval, and I think those were, you know, good suggestions, either physical samples, you know, quality control data.

I think, as we start rolling out self-certification, we will be wanting to have your ideas on how -- you know, what the parameters should be and how we can best evaluate each pilot. They're not all cookie cutters, and I think for the different product areas, there should be different ways to set up the pilot and evaluate it.

MODERATOR CONLEY: A question for Les: Since there continues to be enormous variability in the FDA inspection process, how will you assure that the evaluation of the pilot program via the inspection process is not similarly skewed by the inspector differences? Will the assessment inspections include CBER?

DR. HOLNESS: Yes, the inspections will include CBER, together with the district. So that any problems with an individual inspector probably can be discussed with the inspection team, and the deficiencies can be ironed out or problems can be

ironed out in that manner.

MODERATOR CONLEY: A question for Jong: Do the pilot programs exclude the possibility of approval of comparability protocols on the same subjects? Have we wasted our time in attempting to develop comparability protocols?

DR. LEE: I wouldn't say that any time was wasted in developing a comparability protocol. I think the pilot is not in effect now and, if you have a protocol already developed and ready to be submitted and maybe even being submitted, even being evaluated or have already been submitted, that would be fine.

Simply, you will gain approval through that route rather than the pilot. As for the mutual exclusivity, we have not defined the pilot program, the overall program per se, to really make definite exclusions about anything.

The cornerstone, the key idea behind the pilot program is that we use the self-certification to adherence to a previously prescribed set of licensing criteria as the basis to evaluate -- basis to approve licensure supplements or applications.

So given that basic long term goal and central idea, the individual -- the specifics have not been worked out, but the two pilots that we discussed today under the program is more clearly defined, and we do have to make some clear definitions in order to

make progress and in order to take the first step.

The two specific pilots are geared towards the inspectional process, and the fact that you are submitting a comparability protocol to do anything but prior approval supplementation route indicates that you are trying to obtain approval without a review of a particular plan for demonstrating your reason and justification for down-classifying.

If you have a plan justification and good reasons to down-classify a particular supplemental request from prior approval to anything other than prior approval supplement, then those have to be, obviously, reviewed in order for us to agree with you.

These are -- Comparability protocols are specific proposals that you make to us, and in order for us to agree with you, it has to be reviewed. For that reason, I think, we cannot really subsume comparability protocol into the pilot program as defined today.

I think the whole idea of self-certification to something already published, discussed and agreed upon basically precludes the idea of comparability protocol.

Now it's possible to extend the definition of the pilot program to include this. Right now, I can't think of a way to do that. It's not clear to me how the definition could be expanded to include

comparability protocol and not sacrifice public health. However, maybe -- perhaps some of you have some real bright ideas as to how that could be accomplished.

So in short, I can't see it being part of the pilot as defined today, but in the long term it could be, and that's based on how you propose and justify the idea of combining the two ways of obtaining licensure.

That's a long-winded answer, and it perhaps was more confusing than clarifying.

CAPTAIN GUSTAFSON: Just -- You know, I might add, there were discussions early on on the comparability protocol notion that perhaps -- It's mainly in the drug industry -- that perhaps there could be generic comparability protocols -- you know, templates for a comparability protocol that then could be used by, you know, everyone.

I think that the straight drug section of the industry kind of gave that idea up, that these were very specific manufacturer changes, you know, either as something that would need to have a long development phase but needed to be implemented fairly quickly, and so you would want the FDA to look at a protocol and approve it ahead of time, but then let the change be downgraded to lesser reporting categories so it could be implemented more quickly; or

as I have said before, as use of comparability protocols to more standardize a roll-out of a new manufacturing process in multiple manufacturing facilities.

I think most people have kind of decided that those are pretty manufacturer specific, but you know, there may be times that there might be a generic comparability protocol that then could be picked up and used by others. I think that -- You know, that could be under consideration, but at the time the comparability protocol is a prior approval supplement, but it's not included at least in these two pilots.

These two pilots are -- you know, but as we see them, would have some fairly specific standardization that someone would just agree that they would adhere to the guidance document, and we would then review at inspection to see whether they actually did, and issue the license based on that.

MODERATOR CONLEY: Next question, also for Mary: How will you guard against immortalizing less optimal practices because improvements will be precluded by the "no variation" rule? This change barrier already exists to some extent because of the review process, but it will get worse when you have to wait for a guidance document change. Sad to create barriers to improvement.

CAPTAIN GUSTAFSON: I think this is a very

good question and, of course, it always comes up. You don't want standardization to impede creativity, but on the other hand, there's a lot of things that are done in blood banks and plasma centers that are very well standardized and that don't change a lot over time, and we spent -- You spend a lot of time filing submissions about them, and we spend a lot of time reviewing them.

I think that's the area that we really want to capture under the umbrella of self-certification to a monograph standard. For the innovative ideas, I think there's always going to be the prior approval supplement route where data would be submitted to support a change that is, you know, outside of licensing criteria that we have published.

I think also another issue is how do we keep up on guidance. It's also an issue on how do we keep people's license applications current and state of the art, not only in the blood area but the rest of the biologics.

Investigators will do an inspection of someplace, and they will cite someone for GMP deficiency. They will say, well, we had this approved, it's under our license. When you look, it was approved maybe 12 to 15 years ago.

So there is a need to keep people's licenses current as one issue, and also to keep the

practices, the licensing practices, state of the art. I think, as we develop -- as we roll out the idea of self-certification, we are going to want industry input into guidance documents.

You know, Gil asked earlier today with his questions -- There's a group, Coalition for Regulatory Reform, which has been formed to represent the blood and plasma industry. You know, what are your ideas on perhaps having CFRR set up expert panels for different areas where they could make comments on updates of guidance documents and, you know, have those then come through us and go through the GGP protocol, the process in order to get them published as final guidances.

I think you could probably tell from my slides that we're not going to keep having an influx of staff to write guidances. So we are going to depend more and more on the industry to help us develop standards and licensing criteria.

So I think this is a shared responsibility, to make sure that we keep -- the government keeps up to date on licensing criteria, but also the industry then keeps up to date on their practices.

MODERATOR CONLEY: Jong did a real good job through his talk of letting us know how far we were along in the process. I have 26 cards here, and

we are on Card 7. This will be a question to Les.

To what extent will the overall compliance profile of a company affect their eligibility for pilot program approval?

DR. HOLNESS: Well, basically, you must have an unrevoked, unsuspended license, and other companies that are in other compliance situations will probably dealt with on a case by case basis.

MODERATOR CONLEY: More than ever, you want to have your act together when the FDA comes to visit, because you have certified performance to a standard criteria.

CAPTAIN GUSTAFSON: I might add that we have not proposed limiting the pilot to any particular compliance status, other than having an unsuspended and unrevoked license, and that this would be supplementing it. But as Gil said, I think it behooves anyone, if they know they are under compliance problems, if they're really having difficulties in maintaining compliance, they might not be the best candidate for participation in the pilot; because we will be evaluating the pilot based on the pre-license inspection, and we will be using that to decide how much further to go in this.

MODERATOR CONLEY: I have some mixed concerns. One, I don't want to skew the industry's ability to adhere to a pilot by saying you should

self-select yourself out of the process if you are having trouble. But at the same time, you would not want to enter into a self-certification process without full confidence that you could demonstrate compliance to the base document.

This question will go to Elizabeth, even though it references Dr. Lee's presentation.

What is Dr. Lee's definition of what's included in his category, donor monitoring, i.e., does this include the laboratory methods for antibody detection, identification, and quantitation?

MS. CALLAGHAN: I think that would depend on whether or not you have -- you're doing the identification and everything yourself or whether you're having someone else do it.

I think it's going to be at the discretion of the inspector when they go in, whether or not they want to see who's doing your antibody panels, who's doing your donor monitoring. However, I guess one of the questions we always run into is the cells are picked by our center medical director, and he is the one who makes the decision whether or not the cells should be given.

That's fine and wonderful, and if you have a centralized medical director making these decisions, that's okay. However, the physician at the facility has to have an idea of what's going on in the program.

As I hoped I got across in my talk, this is where we find most of the problems.

The center physicians at each location has no idea of why he's giving these cells, why he should give more, why he shouldn't give them, what he should be evaluating in any kind of adverse responses.

I think one of the things we really have to look at is if the center physician at each location has control of the program, regardless of what the corporate medical director makes a decision about.

Does that answer your question, I hope?

MODERATOR CONLEY: Sure. Ann, would you come to the mike, since we are recording this, and identify yourself for the record.

MS. HOPPE: I guess what I'm asking here is whether a change in a laboratory method would be something that would be covered under the pilot program? For example, we've been waiting nine months to get an improved antibody quantitation method approved, and there's clearly a much better method titrations done manually; but, you know, we're doing things in duplicate. We're spending a lot of money when it's a better method.

Would, under the pilot program, for example, you be able to make that kind of a change? Is that part of donor monitoring, which was listed as one of the things that would be under the pilot

program?

MS. CALLAGHAN: If you're approved for that procedure, I guess it would be okay. I don't -- You know, I guess I'm not quite sure of what you're submissions are.

CAPTAIN GUSTAFSON: If I can butt in -- I think that it's not really included in the pilot at this time. If there are new innovative changes, they would still be a prior approval supplement.

The pilot, as we foresee it, would be a fairly controlled, you know, limited adherence to certain criteria.

MS. HOPPE: So laboratory methods would not be something covered under donor monitoring?

CAPTAIN GUSTAFSON: I think, if there are -- You know, the methods that are ones that are well recognized methods, I think it would be. If it's some new, you know, truly innovative approach to looking at titers or whatever, I think that it would come under a prior approval supplement.

DR. LEE: But if I may add one additional comment, that is not to preclude you from proposing your series of laboratory measurements to be included in the pilot guidance. In other words, we can implement the pilot under the current guidance, once it's finalized, but if you happen to think of a better way to monitor laboratory values and monitor the

donor, you could propose that as possible changes to the pilot guidance, which could be version B of the pilot for the same subject.

MS. HOPPE: Yes, except that's obviously problematic from a proprietary, competitive standpoint, but there have to be things you don't really wish to divulge to the whole world but that are better ways to do things.

DR. LEE: Right. Now if that's the case, in order to protect confidentiality, we obviously cannot have a prescribed, widely publicized, pre-agreed upon set of licensing criteria, but you will have to tell us what you're thinking, and we'll have to agree with you, which almost by the way it's set up cannot obviate a review.

We'll have to review what you're proposing, and that's -- Although that process can be moved along very quickly, depending upon how familiar we are with your proposal and how well you put your application together, I'm afraid the basic concept of the pilot is beyond that.

The concept of the pilot is to move through without necessarily a detailed review, because we have already discussed up front to a set of licensing criteria, and we have already publicly agreed upon that, and we are basing not performing the review on that basis of prior discussion.

Obviously, confidentiality and private discussion are mutually exclusive.

MODERATOR CONLEY: Correct me if I'm wrong, but historically, general laboratory practices such as the testing for infectious disease markers has pretty much fallen in the purview of the field and their routine inspections under CGMP requirements. Those kinds of tests are not typically submitted as part of a CBER review package.

So laboratory practices that are generally followed practices would be inspected under that method, I believe. However, if you are doing things that are new and innovative and, therefore, not generally understood GMPs, then that would have to be a submission.

CAPTAIN GUSTAFSON: I think, you know, in terms of the laboratory procedures where you're using the test kits that have defined manufacturer's directions for use, it's simply GMP. If it's an innovative way of doing something that is not generally recognized as the standard way of performing, it would be innovative, pre-approved -- prior approval supplement.

MODERATOR CONLEY: So if you're going to innovate widely, then you're going to have to submit for FDA approval for the manufacture of a licensed product, and we want to discuss some of that a little

bit more and get some more feedback from you all this afternoon.

The next question is also for Mary. It sounds like this is still a location by location process which appears to conflict with the stated goals of the BLA process which was purported to provide mechanisms for approvals that apply system-wide. Why is the blood area not approaching this in a way more consistent with the BLA objectives?

CAPTAIN GUSTAFSON: Well, I think we are. There's nothing in the biologics licensing application process that precludes facility performance. That's not in any area of drug or biologics approval.

The performance within the manufacturing facility is an important part of the pre-approval process. The establishment of the -- I mean, the elimination of the establishment licensing had to do with not requiring a separate filing for each and every single location.

It does allow lumping in a single filing multiple changes at multiple facilities, but if there's validation data that would need to be submitted and reviewed, that's facility specific, that would still be required to be sent in.

In selecting the two pilot areas, we selected areas specifically where we have retained facility review, because of the variations in the

facilities -- the individual facilities to implement both the irradiation processes and the red cell immunization.

In terms of irradiation, one company may use multiple types of blood irradiators, including linear acceleration, and they may have facilities that do on-site irradiation, and they may have facilities that have contract irradiation, either one of their own facilities or something that's clear out of their organization.

With red cell immunization, I think, if Elizabeth has said it once, she's said it about four dozen times, the primary variable in the facilities in red cell immunization programs is the medical director on-site and the ability of that medical director to perform medical supervision over what is going on in the red cell immunization program.

Not that he has to be the expert on which antigens are on the red cell -- In fact, I think we are more comfortable with having some of those centrally controlled by someone who really understands immunohematology -- but in being able to give informed consent to the donor and, particularly, in being able to answer questions about the red cell immunization program.

So in both of the areas that we have selected, we feel that there are enough facility

variability issues that we are retaining looking at those facility issues.

In other areas, I think we do take a corporate approach. Changes in donor suitability forms and procedures -- we readily feel that a firm can roll out how that question is asked and training on the SOP for the historians.

So, you know, there are particular areas where we do let corporate changes just happen, regardless of the number of facilities, but when it really impacts the individual product because of the individual variability, whether it's because of equipment, personnel training or supervision, we do retain the facility -- looking at the facility issues.

MODERATOR CONLEY: Question for Jong: Please describe in greater detail what the perceived health risks are that led to the cell qualification aspect of red blood cell immunization programs not being included in the pilot program.

DR. LEE: For the cell qualification process, we have to keep in mind that these cells are to be used on donors who will receive absolutely no benefit from receiving those cells as part of the immunization process. So we have a fairly heavy obligation to the donor that the donor receives an immunization and that that donor's health is not compromised.

Unlike a transfusion where a small amount of risk is accepted, based on the return, the greater benefit to -- the medical benefit from the transfusion itself, that's not true for red cell immunization. Donors receive cells, and absolutely no medical benefit, strictly for the purpose of that donor to perform better as a blood donor in the future, i.e., that plasma will contain a particular antibody directed to some selected set of red cell antigens.

For that reason, there are a strict set of criteria built into the cell qualification process. The cells are collected form the donor, and the donor is periodically monitored and is re-qualified at the end of the year. If that donor -- Now I'm talking about the initial donor, way back in the beginning of the process.

When that donor returns after one year and is free of all infectious disease that we anticipate to be problematic for transfusion, then the cells are halfway qualified. However, that's not enough. We feel that that's not enough cell qualification because of the obligation to protect the donor who has no medical benefit.

So once that cell has been halfway qualified, then those cells are then used in up to, but no more, than three other donors or, in this case, I should refer to these donors as immunization

recipients. Then those donors are in turn followed for another year.

So we have the initial year plus a secondary year spent on maximum of three donors. If all testing is negative throughout the period of two years, then we have pretty good confidence that these cells which were collected two years ago and cryopreserved is indeed fairly safe, and we deem them qualified.

Now because of this lengthy process of cell qualification, it does not lend itself well to the idea of self-certification for the purpose of reducing reporting burden or saving time in terms of receiving CBER approval. You will have to wait two years anyway once you begin the process, and it is the standard operating procedures that is being discussed here.

Once you have a set of procedures in place, you could simply send it in to us and let us review over the two-year period, and it doesn't really matter when we get back to you, I suppose, in this particular instance, because you have to wait two years anyway.

So that's part of the reason why the cell qualification process was excluded. Number one, it's not going to be of much interest to you if you understand what we are talking about precisely.

Secondly, the public health impact, the obligation that we have to the donor and the obligation that we have to protect the plasma that's collected from all donors once cells are deemed qualified.

Once they're qualified, then they can be used on any donor under the program without further monitoring of the cells, because these cells have been quarantined for two years and everything cleared, and this is analogous to the FSP donor re-tested idea, basically re-testing the donor to make sure that the product is of optimal safety.

If we were to simply allow self-certification to the fact that the cells are qualified, I think we are taking too much on leap of faith; and basically, again for those two reasons, to optimally protect the donor as well as the subsequent products collected from the donor, and in the interest of you as an applicant in saving time in receiving CBER approval, we have elected not to include that portion of the red blood cell immunization program under the pilot.

I can't seem to answer any question with short, clear sentences.

MODERATOR CONLEY: We're on card 11 of 26, and this one snuck in two questions. The second question I'm going to add to the second card. It's a

similar question. I'm going to ask Judy Ciaraldi to come to one of the microphones on the floor or at the table, because she's been involved in a CBER committee looking at this.

The question says: What does a comparability protocol look like?

MS. CIARALDI: Can everybody hear me? Okay.

Jong and Mary have both described or summarized what a comparability protocol is. What I'm going to do is just take all their information and put it together in some bullets to try to consolidate what a comparability protocol is.

To answer specifically what it is, it's a set of paper -- that's what it looks like. But to get on beyond that, a full discussion of comparability protocol is beyond the scope of this workshop but, as I said, I'll define it in some bullets.

Comparability protocol is another option of submitting supplements or reporting changes to your approved application. It's described in the newly revised 21 CFR 601.12. So you can see a description of it in there.

The filing of a comparability protocol may allow for in the future -- when implementing that change that's approved on the comparability protocol, you may be able to report it in a lower reporting

category, and you may be able to implement the change a little bit more quickly than you would originally.

To define a comparability protocol, it is a protocol or a group of procedures, a set of standards that describes in detail the implementation of a specific process or the implementation of the specific change that you want to report or that you want to perform.

A comparability protocol includes things like procedures, acceptance criteria for determining the acceptability or the effectiveness of the change, validation methods data and a variety of other things that are listed in that Code of Federal Regulations 601.12.

The comparability protocol initially is submitted as a prior approval supplement, a PAS. We will review all of the procedures. We will review all of the data, everything that is submitted that you have given us to describe what you're going to do to implement the change, determine that you've implemented it in a proper procedure.

If we have approved your comparability protocol, when you implement that change in the future, then you can report that change that you've implemented to us in a lower reporting category. For instance, if it was originally a change that fell into the prior approval supplement category and in our

approval letter we tell you your comparability protocol is approved and in the future you may report this change to us under the CBE 30 reporting category, as you implement the change then you just report it to us as a change that's being effected in 30 days and you may start doing the change within -- and submitting products prepared under the change within 30 days after we've received your notification of the change or your supplement showing us your change.

A description of a comparability protocol is included in the guidance document that Mary told you about. As she said, the general guidance document for describing the 601.12 for the biologics was a little druggy, and I had to agree with her. You as an industry complained and said we need something in our own language.

So we are actively working on that, and it includes a section on the comparability protocol for blood and plasma products. The Center is also working very hard on developing a general guidance document on comparability protocols. It will include in a little more detail the specifics of what goes into putting together a comparability protocol package for submission.

If you do have specific questions on comparability protocols, please don't hesitate to send them in or to -- by FAX or, you know, by letter or

please phone us, and we'll be glad to answer your specific comparability protocol questions.

Has that answered a little bit more of what a comparability protocol is? Thank you.

MODERATOR CONLEY: Change processing and shifting paradigms or whatever you want to call it, we're all in the midst of it. I liked the one slide earlier today that showed the tightrope walk between two points, because we're definitely in the midst of a lot of transition and, hopefully, we'll come out on the other end with everything being a lot clearer for all of us.

Okay, I'm going to combine the second question on this card and a second one. This goes to Mary Ann. They're pretty much on the same topic.

On the first card: Under the pilot program for Gamma irradiation, would a participant already licensed for irradiating red blood cells need to be inspected if supplementing their license to include irradiated platelets or any other component?

The second card reads: If a facility is currently licensed for both red blood cells irradiated and red blood cells leukocytes reduced, under which license should a supplement for red blood cells irradiated/leukocytes reduced be submitted, if the above supplement is the above supplement, just a submission of appropriate labels?

MS. DENHAM: Well, if you're licensed for Gamma irradiation, you are licensed for the process. So, basically, if you had gotten approval for red blood cells irradiated or red blood cells leuko reduced irradiated, then you can just send in the labels for the others for label review.

So that's basically, if you've already been licensed for Gamma irradiation and you want to add other products, then you can just send in your labels for label review.

MODERATOR CONLEY: Okay. This is for Jong, two questions:

Will pre-license inspections be the cornerstone of all self-certifications?

DR. LEE: Well, it's certainly the cornerstone of the two specific pilots described today, but that doesn't necessarily mean that it will remain the cornerstone of the entire program.

As we referred to in prior presentations, the program is a bigger concept, has one firm basic idea in mind -- that is, to allow self-certification for adherence to a set of pre-agreed upon licensing criteria. That's the basic concept. However, beyond that basic concept, exactly how to administer or evolve the program is unclear.

Obviously, we have to start somewhere, and we've chosen two specific areas where we can make some

concrete statements about how we're going to implement this program and, as defined for the two specific pilots, it does remain the cornerstone. However, the pre-license inspection or pre-approval inspection may or may not be omitted, depending upon the experience we gain under this current pilot and depending upon the level of interest and your arguments to back up whatever you propose.

Quite possibly, we could use the routine inspection as a way to get around the pre-license inspections, since routine inspections are being performed biannually all the time anyway. However, that also raises a set of complications which must be carefully considered.

So in summary, I would say it does not necessarily have to remain the cornerstone of the entire program, but it does so for the two specific pilots described today.

MODERATOR CONLEY: On the same card it goes on with a comment/question/concern. I want to say .com, but --

Timeliness of availability of guidance, especially given the fact that the guidances need to go through good guidance practice issued prior to being finalized, may as well do a straight submission.

It's not a question. Do you want to comment on that, Jong?

DR. LEE: Okay. That's true. If you have something ready to go right now, might as well send it in under the traditional way of doing things, because that's the only route available to us today, and might as well start moving forward; because you don't know when this pilot program is actually going to be implemented, although we have some good expectations about timelines.

I wouldn't necessarily say I'll just wait until it gets effective, because you might be unpleasantly surprised.

That statement is true for as it is today. However, a year from now after the program has actually been implemented, then you have a choice of pursuing the routine route or actually taking advantage of the speed that the option -- the prior approval supplement option will afford you under the pilot.

So I would say at this point, it's not of immediate benefit to you, but it will be of benefit, and we anticipate it to be in the very near future.

MODERATOR CONLEY: With that answer, we mark the halfway point in the cards. I congratulate the audience for staying awake. A few of you, would you please pour a glass of ice cold water, hand it to the person next to you. There are a few that are having trouble hanging on. Come on, we're going to

plow ahead.

Under additional pilot requirements -- and it says page 7, last point -- IRBC and SP donors tested for ABO, Rh, K, Fy(a), Fy(b), Jk(a) and Jk(b), the question is -- and I think this may allude to what Mary was talking about earlier, people who have SOPs that may have been approved years ago.

The question is: Will facilities that are using approved SOPs that are not testing for FY(b), Jk(a) and Jk(b) be required to test for these newly added antigens?

MS. CALLAGHAN: If they're going to be part of the pilot program, yes; and if you're not testing, why?

CAPTAIN GUSTAFSON: This is one of those things where keeping up with state of the art is important. When we were discussing this guidance, we really thought that, even though the old guidance didn't include all of this, that by looking at what has come into us and, you know, SOP changes and all, that we clearly thought that the industry had moved to doing all of the testing that is reflected in Elizabeth's presentation.

MODERATOR CONLEY: This one probably also goes to Elizabeth: Does the agency require any notification prior to immunizing the five donors required for pre-license inspection?

MS. CALLAGHAN: Notification to us, I assume, is what you're talking about.

MODERATOR CONLEY: Yes.

MS. CALLAGHAN: Okay. If you are going to be participating in the pilot program -- and remember, we're not implementing the programs just yet, but if you're going to be participating in the program, no, you do not have to notify us when you start immunizing. However, you do have to have at least five people participating in the program when you send it in and be ready for inspection.

CAPTAIN GUSTAFSON: You know, going into a program like this, we take some risks as well as you taking some risks. This is one area that we have had considerable discussion about, but as part of this self-certification, once the guidance is finalized, you would be expected to be in conformance with that guidance under the pilot before you immunized anybody.

So -- but in terms of advising us and setting up the inspection, no, you could already institute to prepare yourself for your pre-license inspection by following the guidance. But don't do it yet, not until a final guidance, and not unless you actually intend on filing a supplement for red cell immunization program. We don't want people just out there sticking people with red cells. Yes, Ann?

MS. HOPPE: At what point does the product

become saleable then?

CAPTAIN GUSTAFSON: At the point you started collecting the product under the pilot, if in fact you get approval.

MODERATOR CONLEY: When the approval is received from FDA following the on-site inspection in the pilot program, the product would be saleable. Correct?

CAPTAIN GUSTAFSON: Yes. Yes, and it would include everything that you had, that you had made under your plan of self-certification. I mean, we're giving a lot on this as well as --

MS. HOPPE: I'm missing something. What are you gaining by this pilot program if nothing happens until after the inspection?

CAPTAIN GUSTAFSON: What you're gaining is not having an in depth review by FDA prior to having your inspection done, an in depth review of your SOPs. But still it is a prior approval supplement. You could not ship product until you actually received approval.

DR. LEE: I'm glad you asked that question, because I wasn't sure if that point was adequately made clear in the presentations.

The two pilot, specific pilots, that we have selected have two review elements to it, the review of the submission followed by the pre-approval

inspection.

What the two specific pilots propose to do is to abbreviate or just about eliminate at least one element of the two processes; that is, the up front review of the submission, and go right into the pre-approval inspection.

Again, that's speaking from the standpoint of the two specific pilots, and that's not necessarily the way it's going to be throughout the program. That's going to evolve as we find out how we should expand it.

As defined today, you gain by not having to submit a detailed SOP, which will take some time for it to be reviewed and "preliminary approved" enough to move forward with the inspectional aspect of it.

Now if you think that having to wait for five donors is going to be a time consuming process during which you can have your submission sent in to the agency and reviewed and the thing is already moving forward anyway -- if that's your concern, that's a very good concern, and exactly we have grappled with that point.

We have thought about whether or not the requirement -- the traditional requirement of five donor immunization experience is too lengthy to be of timesaving benefit to you, and we have thought about

the idea of reducing that number to possibly three or any number that you think is justified from a public health standpoint.

This is again where we need your comments. Tell us what the number ought to be. Tell us why, and tell us your justification for it, and it may or may not make its way into the next version, next draft of the pilot guidance, which at the current point is headed towards five donor immunization requirement.

CAPTAIN GUSTAFSON: I think, in terms of the pilot, we are talking smaller steps first, but in terms of the overall concept of self-certification licensing, I think we're willing to look at an entire scenario that may involve a deemed approval as soon as you submit a self-certification.

We're not ready for that. I mean, this is going to be a step-wise process, but you know, the initial steps are -- The pilot, definitely we have to have something that we can evaluate in order to determine whether we want to go further with this, whether it is a viable concept.

DR. LEE; I think, basically, what you're saying is that the targeted pilot, specific pilot, for the red cell immunization program does not ideally meet all the criteria that one would like in a pilot such as this, and that's true. But I think that's the best we can find at the moment and the best starting

point.

I don't think you will ever come across an ideal situation, no matter what you do.

MODERATOR CONLEY: Card 16: If immunogen red blood cells are not purchased but are produced internally following all regulatory requirements, can the institution still participate in the pilot program? Elizabeth, I guess.

MS. CALLAGHAN: I guess I'm kind of confused. If you're already producing your own red blood cells, you must already have a license. So why do you have to participate in the pilot program?

I don't know who wrote this question, but could you clarify it for me, please?

MODERATOR CONLEY: Could you clarify the question?

CAPTAIN GUSTAFSON: Well, I think one of the issues is do you have to buy it from an outside source or internally, if you have in another part of the country a facility that's already approved within your organization to prepare the cells, can another facility on the other side of the country get those cells; and the answer is yes.

It doesn't have to be an outside contracting situation. It can be, you know, internal adding a new facility that's using your own cells.

MS. CALLAGHAN: I guess we tried to

clarify that by saying a licensed supplier. So, obviously, if you have another facility that's licensed under the same number you are, it's a licensed supplier.

CAPTAIN GUSTAFSON: But the key is that it can't be a new red cell program. I mean, you would need to use cells that are prepared by someone who is already approved, whether it's another one of your facilities or an outside source.

MODERATOR CONLEY: The next question I will mention, but I will set aside, because really it enters the next set of discussion, which is what should we consider adding to the program next.

The question was: Would you consider a pilot program for licensing red blood cell suppliers? This would be useful. So I'm going to set that side, because that may be one of the next things that we consider for the program.

Card 18: Please repeat the list stating requirements to be in the informed consent forms for red blood cell recipients that were discussed in Ms. Callaghan's talk.

MS. CALLAGHAN: I really think you should wait until the pilot program and the guidance becomes available. It all will be enumerated in there. I don't think anybody wants to hear that one over again. But it will be in the guidance document.

MODERATOR CONLEY: Stay tuned. Judy is sneaking more cards in here. Our goal is now 30 cards. Stay awake a little longer. Hang with me.

AUDIENCE PARTICIPANT: Shoot the messenger.

MODERATOR CONLEY: It's her. It's her. Why am I compulsively counting cards?

When is the red blood cell immunization program guidance expected to be available? When is BLA expected to be ready for blood? Does FDA plan to list the approved providers of immunogen red blood cells?

I'll answer the BLA question. For BLA, the final rule is back at FDA. I know we have a meeting next week to discuss the comments on the BLA rule. When we are done with the comments and publish it as a final rule, that will settle BLA.

For blood and blood components, you will begin to use the 356h and begin to refer to supplementing your biologics license application when the CMC guidance documents is published in final form. That -- Again, the comment period is closed. There are three comments sitting in a folder on my desk, and hopefully, in the first quarter of next year we'll be getting to that, and that will be published.

So then back to questions 1 and 3 on this card: When is the red blood cell immunization program

guidance expected to be available?

CAPTAIN GUSTAFSON: Well, it's a few months behind the one that we just got out on the Web yesterday. So I would say, you know --

MODERATOR CONLEY: Stay tuned.

CAPTAIN GUSTAFSON: Yes, stay tuned, but I'd say between March and June, a draft. Even though the docket is not open you have the cite that Elizabeth had today. I mean, we're willing to take your comments, even your written comments, you know, based on this workshop.

DR. LEE: If you noticed, Elizabeth's and Mary Ann's slides were quite full of words, and that was by design; because although -- well, at least for the irradiation document, it's already out, but at the time we prepared the workshop packet we anticipated it not being out, and we had thought that it was -- it might be premature to release even the draft version in a public way. But we still tried to capture all the information in a way that's useful to you.

In an effort to include as much detail, specific detail, as possible so that it can be of use, the slides became very wordy. So the irradiation document is behind the other document. Its current thinking stage is not enough to allow it to be shared directly, but the slide content reveals our current thinking, and the best time to influence our current

thinking is at the inception stage.

MODERATOR CONLEY: And the last question from the same card: Does FDA plan to list approved providers of immunogen red blood cells?

CAPTAIN GUSTAFSON: No, we don't. I think that is a breach of confidentiality.

MODERATOR CONLEY: How does the inspection for a supplement such as the irradiation pilot affect the regular annual inspection process? Is the supplement inspection performed by field investigators or for the pilot by FDA headquarters personnel?

DR. HOLNESS: Well, as I mentioned before, it will be performed by headquarters personnel with -- the district will be invited. So it will be both. It will be a team inspection with both headquarters and district.

MODERATOR CONLEY: Once you have completed this initial pilot, would you consider accepting applications based on a facility's track record in meeting GMP requirements instead of specifying products that it can be used for?

In other words, what we presented today -- I think the question is asking we've presented a product by product release of a new program, a self-certification program. They're asking if the gates can be thrown open a little wider so that somebody who wants to do something new would be judged largely on

their history of GMP compliance.

DR. LEE: Well, I guess what you're saying is can the pre-licensing inspection be eliminated based on track record. We have no plans of doing so under the current pilot as described today.

I think what you're talking about is more closely along the lines of a comparability protocol where you could propose to us -- which will have to be submitted and evaluated and, therefore, it falls out of the pilot program, but it's still of benefit to you; because it will save you time and reporting burden in a different route.

You could propose to us that you've done this, this, this and this, and therefore, we've eliminated substantial risks and have been able to reduce what's perceived as major risk to some other lower risk, moderate or minor, and you tell us what you did, what the effect was, why the rationale is sound, and if that's the case, then it's conceivable that you might receive approval in a broader fashion for many facilities rather than facility by facility approach.

Sounds like you're approaching the idea of a comparability protocol there rather than the pilot program. Now keep in mind, all of the various streamlining initiatives are different tools of reducing burden while protecting public health at the

same time, and just because we are here talking about the pilot program doesn't mean we have to use that tool to achieve every -- and that you see around you, just because you have a hammer in your hand doesn't have to -- you don't mean that you always have to use the hammer to pound in a screw. You might use a screwdriver.

We're trying to come up with various ways, and we've added one more to existing methods and that's the changes to be reported, the BLA initiative and the pilot program under the changes reported, to allow more -- greater and greater flexibility in achieving the same goal of reducing reporting burden while protecting public safety.

MODERATOR CONLEY: The next question is regarding immunization: Are already approved 640.120 variances revoked if they conflict with what was on the slides as required for red blood cell immunizations; i.e., to participate in the pilot under the stated requirements, we would appear to lose ground. Why should this be necessary?

CAPTAIN GUSTAFSON: I'm not sure of the specifics of this case, but if you have a 640.120 that's approved -- you know, a variance to something that's approved, that's not revoked just because we set up a pilot program that had a set of criteria that doesn't include what you happen to be doing.

The pilot, as we foresee, would be somewhat restrictive in the licensing criteria, because it would be a standard approach that you would self-certify that you're following the standard approach. However, there's always the option that, if you want to do something really different, you know, you file it as a regular supplement approval.

I hope that's answered the question, because what we have proposed so far in these guidances would be one way of doing either of these types of operations, and by the review of the applications that we have seen, it is the primary way that the industry is performing these operations.

So that's why we would develop it as a standardized approach, that if someone wanted to self-certify, that they would against this approach. It doesn't say that that's the only way that you can do red cell immunization or it's the only way that you can perform irradiation.

You know, we will review other ways of doing it, but what we foresee as a pilot now would be a somewhat restrictive category in order to limit the variables. But you know, your comments on this are more than welcome.

MODERATOR CONLEY: I think we have a nice mixed group here today, because we have plasma people that aren't usually concerned about irradiation. We

likely have red cell and whole blood people who aren't usually immunizing donors.

I suspect it's the root of this question: How can receipt of documents include five donors already in a program if this is a new program for that center? Elizabeth?

MS. CALLAGHAN: I guess I'm not quite sure what you mean by receipt of --

MODERATOR CONLEY: Part of the submission requires the five donors, even though it's not an approved program.

MS. CALLAGHAN: I'm sorry. I wasn't listening. When you apply to this program under the pilot, you should have five donors participating in your program, and as part of starting up this program -- and you must realize that you self-certify that I am doing everything according to the protocols within the pilot, and you have five people participating.

Then you tell us I have five people participating, please come out and inspect, and that's what we do. I guess I don't understand why they shouldn't be there.

DR. LEE; I guess, if you keep in mind the fact that a meaningful review -- a meaningful inspection, pre-approval inspection, cannot be performed unless there is donor immunization already going on.

So if you tell us that you're inspection ready because you already implemented all the SOPs according to the criteria outlined in the pilot guidances, then you're certifying to us that you are inspection ready; and unless you have donors already in there, we cannot assess from an inspectional standpoint.

MODERATOR CONLEY: Yes, Judy?

MS. CIARALDI; I just want to add a question that might help direct your responses. Can they not apply first and -- you know, the time that they submit their self-certification, and then be rejected for the pilot? Not everybody that requests participation in the pilot, you know, is accepted. I mean, there are times when we could reject some people. Would that ever happen?

CAPTAIN GUSTAFSON: Well, I think, you know, if the inspection showed that they were not actually adhering to the guidance, we would revert them to a regular review, and we would want to look at their SOPs.

I guess, you know, the issue -- The difference would be are they just doing acceptable alternatives or are they really out of compliance from a GMP standpoint? The former would kick them out of the pilot, but not kick them out of licensing for red blood cell immunization.

The latter might, in fact, mean that your work is in vain. You may have problems that would preclude you being able to be approved for red cell immunization program.

MODERATOR CONLEY: Did we adequately answer that question? Does anybody want more clarification?

MS. HOPPE: I guess that seems a little inconsistent where currently you have to wait for a reference number before you can do the first immunization, and here you're saying you have to have at least five people. Finally, if you've done one, you have to manage to find five. So you may have been running this program for months before you send in your first piece of paper.

I guess industry shouldn't complain about that, but it does make you wonder.

MS. CALLAGHAN: Well, I mean it is one area that we were willing to take a risk on, and you know, I think by looking at our inventory that one of the problems maybe is that you're having trouble finding the donors to immunize, not that our review of all of the paperwork is holding you up.

So that may be the apparent inconsistency in this, but you know, if, you know, you go into a new area. You have five donors that are thrown in your lap that you can look at a guidance document and say

I'm doing all of this, and start immunizing them tomorrow and send in your self-certification for your inspection within 90 days, I mean, you would be the perfect candidate for this pilot.

Maybe that's not what's happening out there. It may be taking you a lot longer to find donors who are willing to participate. So the actual review process is not what's holding you up.

We would be interested to hear that as well. I mean, maybe this is not the pilot area for the plasma folks, but you know, we want to hear your thoughts. You know, we were seeing a lot of submissions for supplements for red cell immunization, and that's one reason why we selected this, and most of them were being contract immunization facilities.

So we thought, well, maybe this is an area where we can really facilitate the industry being able to incorporate this into their programs through a self-certification. You know, if it's not, tell us. Give us ideas on another area.

MS. HOPPE: Well, I think the difficulty is that the vast amount of time spent in the process is waiting for a pre-license inspection and waiting for what happens after, and this doesn't seem to address things. As it happens, the review process is pretty good.

You guys have made a lot of very positive

changes on the review process itself, but the pre-license inspection part and the post-pre-license inspection is a killer.

MS. CALLAGHAN: Well, I guess what we have seen with the red cell immunization is right now we have an inventory of places that we've been ready to inspect for, some of them, a year and a half, and the firms have asked us not to come.

So -- and of course, when we set out to talk about this pilot, we only knew of having lots and lots of supplement submissions, and we were trying to figure out a way to cut down the burden of that. But it seems perhaps not to be, you know, the real problem, and we do want to hear your ideas on that.

Maybe if there are areas that would be better to pilot, areas that are more standardized, areas that are more cookie cutter, that what you think are no-brainers that we shouldn't be looking at at all, let us know that.

DR. LEE; It is our hope that the efficiency that we gain by not reviewing the detailed SOP can be diverted to actually performing the joint district/CBER inspections.

Also, in terms of justification for not going through the reference numb er assignment process, we're banking on the fact that by starting with cells that have already been qualified from a

licensed supplier and banking on the fact that you are able to adhere to CBER criteria in terms of actual donor immunization, that gives us equivalent protection that is substitutable for the reference number assignment process, because the submission is reviewed enough to allow the immunizations to go on.

So I think omitting the reference number step in terms of allowing the process to move forward -- we have basically provided alternate means of affording the same public health safety level while omitting the review. And in terms of the inspectional concern, that's why I had that question mark under resources.

Inspectional resources has always been a problem, and we're not so sure if we can meet our own expectations, guarded expectations at this point, but there is some efficiency gained by not performing the review, and our reviewers will probably spend more time in the future as a part of the pre-licensing inspection team rather than submission review alone.

MODERATOR CONLEY: I will remind all of you that we are using a transcriptionist, and so that the record of the meeting is complete, please use the microphones when making comments, and these microphones in the center are portable. So we can bring them to you, if need be.

Okay. We're on card 24 of 31. I will

encourage everybody to abbreviate their answers, so that we can get a break at 2:30.

Instead of identifying a change that has already reached a peak in applications, why not validate this pilot with one for which a real impact can be seen, such as the upcoming move for leukocyte reduction of blood products? That would be something that you can really get data for and see if it is effective.

CAPTAIN GUSTAFSON: That's a good idea. Obviously, we didn't know where the world is going on leuko reduction when we first set out to do the pilot, but whoever commented on that, I think you're right. I think the industry is at this point going to be moving towards universal leuko reduction.

A lot of the industry is already approved for leuko reduction, though. So, you know, it may be not as big of an issue. I don't know, but the comment is very well received, and thank you.

DR. LEE; Obviously, to every good suggestion, there is a downside. It's not clear how we will evaluate the impact if we move directly to self-certification of leuko-reduction. As it's being currently done now, the submission is reviewed for controls built in to assure safety of the actual -- safety and efficacy of the actual leuko-reduced product.

If we were to abbreviate that process, then how will we know that we've done the right thing? There is no inspection element traditionally for the review of leuko-reduction submissions. If the proposal is to include replace inspection in lieu of submission review rather than simply abbreviating submission review, that's a viable alternative. However, it sort of defeats the purpose of gaining time and reducing the reporting burden.

So it's a good process, but then again, it seems to fall somewhat outside the scope of the spirit of the pilot program.

Sorry, though, I didn't mean to make my answer so long.

CAPTAIN GUSTAFSON: Yes, rain on her parade, Jong. I think what we will need to do is go back and see, you know, what percent of the industry is already licensed for leuko-reduction; and if you could, you know, think of maybe evaluation criteria that we could use in a pilot -- Like Jong said, we don't inspect facilities now for a leuko-reduction supplement. We look at it in terms of the controls and process and the data.

We're open to suggestions on that.

MODERATOR CONLEY: For facilities that want to be part of the pilot, could the FDA submit a checklist that the facility could use to prepare for

the pre-assessment inspection?

DR. LEE: Well, first of all, such a checklist already exists, and what we are hoping to accomplish through the specific pilot is that we have a document that's better than the checklist.

It will tell you exactly how to -- It's difficult to convert the checklist into your standard operating procedure, which has to be institution specific, and we can't simply take your word for it that you've done the right conversion.

The checklist is a very cursory, bullet-line overview of things that we would look for. Obviously, all the details are filled in by the individual reviewers at the review stage.

Since there is too much of a question mark in using simply the checklist, what we are proposing here are specific pilot guidances which will lend itself better to a self-conversion to an institution specific SOP.

So such a checklist already exists, but it doesn't fit the purpose of the pilot program, and that's why we are beginning to implement specific pilots using pilot guidances as monographs as improved versions of the checklist.

CAPTAIN GUSTAFSON: If I could add a little bit to that, because we have a bureaucratic reason also. I mean, the reviewers, obviously, use

internal checklists to determine whether they have performed a complete review of submissions, to make sure that they have gotten all of the major categories, but it's not a detailed enough checklist to truly be a guidance.

There's another issue with us developing a checklist that you would fill out. That becomes a form, and a form has to have OMB clearance with reporting burden evaluated and a justification for that form being made.

So, you know, there's other problems with using kind of the checklist form rather than a guidance under the good guidance practices. But I think, as Jong said, I think we're trying to get to more detail in the guidance than we would have in a checklist. But I think one of the areas that we would want your comments on is how much detail do you think you need in a self-certification standard?

MODERATOR CONLEY: And we'll take that up after the break.

Using the Gamma irradiation pilot, what would be included in a firm's initial submission to CBER?

A second question on the same card: Assuming the pilot becomes available to the public, would 483 citations on inspection require submission of a complete BLA submission?

So, first, what's included in the initial submission?

MS. DENHAM: Well, basically, it's the same as Les mentioned in his talk, the 356h when that's available. Right now, it's the PLA. Then you would have your self-certification, and that's basically -- well, and a request for the variance under 640.120, and labels. Actually, yours isn't a -- Yeah, yours is a variance. They all are variance.

All the pilots are a variance under 640.120. So it's a request for the variance, the labels, the regular form, whether it's the PLA or the 356h, and the self-certification statement that you meet the criteria.

CAPTAIN GUSTAFSON: And there have been a lot of questions on why are we retaining the label reviews. One of the big reasons for that is because of the transition to the ISBT-128, and there's not a one to one transition between coda bar and ISBT-128.

You're seeing that, and we're seeing it in terms of review. So I think, in order to make that transition as smooth as possible, we want to retain the label review function during that transition period.

MODERATOR CONLEY: And the second part of that question, assuming the pilot becomes available for the public, would 483 citations on inspection

require submission of a complete BLA submission? I'll field that, because it seems like it's asking two things.

Anything that's reported on a 483 is discoverable under Freedom of Information. So as that information, 483s from your inspections is typically available, this information would be available. If the citations are sufficiently severe, and we really haven't determined what that means yet, then you would be asked to step out of the pilot program and submit through normal prior approval supplement CBER review process.

CAPTAIN GUSTAFSON: But it's the same process under a regular inspection now. If you have a pre-license inspection, the inspector who did the inspection reviews the response to the 483 to see if that's adequate to get a license. So it would be a similar type thing.

If the inspector didn't feel that the response was adequate, then we would ask for a regular PAS.

MODERATOR CONLEY: Card 27 of 31: I have a very difficult time locating Web sites and pages to find guidelines and Federal Registry. Have we reached a moment in time that, if you don't surf for changes, you come up lacking with FDA? This is unsatisfactory.

Again, I'll comment to that, because I

find the Web easier to use than my bookshelf. If you find the CBER Home Page, there are what's new items that you can click on that will discuss the availability of CBER related documents.

True, there are Federal Register announcements that aren't necessarily announced on those pages, but again your professional organizations generally do an excellent job of informing you when these things are available.

I don't know if anyone else wants to comment or not. It's a matter of becoming familiar with the Web pages you use most often.

CAPTAIN GUSTAFSON: Well, we had an open public hearing for the device action plan, and I guess it was just last week. It seems like about a month ago now, so much has gone on.

Some of the comments from that meeting, too -- they weren't -- I mean, weren't really complaints about the CBER Web page, because I think people are appreciative of having the information available, but said that it wasn't as user friendly as the Center for Devices and Radiological Health Web page.

I think we did have people from the OCTMA group that monitors the Web page, and I think they did hear that. So I can't tell you that changes will be made. Quite frankly, you know, I'm appreciative of

the CBER Web page and the ability to go online and find things without trying to figure out where in the world I may have filed a piece of paper. But, obviously, the Center for Biologics is more than -- will be more than agreeable to look at ways to make this electronic source more user friendly.

DR. LEE: I guess the concern is that, through the sophisticated use of the computer network, you've converted what at one point had been a passive process to an active one in which, unless you think of looking on your own, you're left out. Whereas, before you got a piece of guidance document or whatever in your mail. And that's true, but I don't think that's a burden that's overly cumbersome in trying to regularly visit the Web site.

CAPTAIN GUSTAFSON: Yes, the individual mailings throughout the year of guidance documents is just not going to happen anymore. You know, due to the ability to have electronic -- and that's not just the Web site. I mean, you can have the FAX-back as well, but also the expense of the individual mailings is something that we can no longer shoulder.

DR. LEE: Also, it forces you to take active participation in the process rather than just sitting back and taking in what the agency announces.

MODERATOR CONLEY: One of the speakers mentioned that titers must be done after every

immunization, which is a new criteria, not part of all currently approved licenses. High red blood cell titers don't hurt donors. What is the FDA's concern?

MS. CALLAGHAN: As part of the pilot program, you should be monitoring what your antibody titers are on your donors. Obviously, if you're immunizing a donor and they reach a plateau of 2,000 -- a titer of 2,000, and you can't get them to respond anymore, should you continue giving red cells and exposing this donor to possible infectious disease or possibly to forming an alloantibody?

This is something that the medical director has to make a decision about. I should think you would be monitoring your donors as far as their titer levels go so you know whether or not you should continue to immunize or if they do need a booster, and it is part of the pilot program, regardless of what you are approved for before.

MODERATOR CONLEY: Okay. I have three cards left, two of which I'm going to answer and, if anybody on the panel thinks that I've answered wrong, they will correct me when you come back. So be sure you come back and find out if I was right. The third one I'm also going to use as kind of a lead-in for our discussion when we return, because I think we're going to come to probably the most important of the day after a break.

First, is a facility -- If a facility wants to participate in a pilot, who should be notified at CBER?

Once these documents publish in final form, you will apply to the same CSO you always have. If you just want to do so to show interest in the pilot program so that we know that there's interest in the industry, then again call the CSO that you normally deal with and express your interest, and we'll be sure to keep track of that information.

Next, can the FDA afford to do this new program? You are adding travel, hotel and food expenses that currently are not being paid to CBER staff.

Again, it is a pilot. Whether pre-license inspections would remain part of this issue as we go on, I don't know if that burden of cost will continue to be there or not. Right now, quite frankly, it's just a matter which pocket it comes out of, and most inspectional issues are coming out of somebody else's pocket, but I doubt that in the long run that that would be allowed to go on, that we're robbing Peter to pay Paul.

So you're right. It is a cost concern, but it is a pilot program that may not stay in the same format in the future.

When we come back, one of the things I'd

like to hear discussed further with the people in the group as well as the panel is this statement: Isn't letting the industry write regulatory guidance and provide self-certification a conflict of interest, and is this really serving the public interest?

So that would be a good place to head off when we come back. We'll take a 15 minute break. We'll reconvene at ten of. Please come back. If you can't come back, though, fill out the evaluation forms, and I hope you participate as well the rest of the day as you did on the questions. Thank you.

(Whereupon, the foregoing matter went off the record at 2:40 p.m. and went back on the record at 2:58 p.m.)

MODERATOR CONLEY: Okay, let's everybody grab your cookie and your caffeine, whether it's carbonated or out of the coffee pot, settle down, and we'll get moving again.

In regards to some of the questions that we were doing right at the close of the session before the break, it was pointed out to me that, at least for the two items that are proposed for the pilot, we do on-site inspections anyway, and they have always been -- included CBER personnel from our office.

So there is no additional expense at this level of the pilot. As the program may expand into new arenas and we may consider evaluating performance

through different ways, those may be issues to consider.

Since we're kind of entering into the brainstorming section of the meeting where we want to share ideas back and forth, we can share things. I don't want at this point to imply the things that we discussed as possible future courses are FDA policy or it's a direction we're definitely going.

Being at the FDA about three and a half years now and doing more and more public speaking, I've been very impressed with the -- impressed may not be the word; frighten may be the word -- by the fact that when you stand behind the podium and you're from the FDA, you may read in the next week that "according to an FDA representative."

So I find that my lectures, I write an awful lot and ask two or three people to look at them, and then I'm afraid to expound too much behind the podium, because I don't want to be setting FDA policy. It's not supposed to be the way we do it. It's done through public hearings and opportunities for comment.

So we have a lot of things to discuss, and we'll go back to the questions that we posed earlier to open things up. Now I have a lavaliere mike up here, and these mikes that are down here in the center are portable. If I have to, I'll play Phil Donahue in order to get you to talk, but hopefully, you'll come

to the mikes on your own.

I will remind you that the transcript is being produced. So, please, do come to the microphone to speak, identify yourself so that that is captured in the record.

If you want to come to the mike and say -- you don't want to identify yourself and you're speaking off the record, but you want the FDA to hear, we'll do that, too. It's important that we hear from you.

Why don't we start with this last question. Isn't letting the industry write regulatory guidance and provide self-certification conflict of interest, and is this really serving public interest?

That really comes to the first question that we posed for possible consideration. Can we turn on the slide projector, please?

Is the concept of self-certification viable? So let's -- I know some people on the panel might want to comment on this, but can we hear somebody? Is there such a conflict of interest built into self-certification that it's not viable? That's not meant to be a yes or no.

CAPTAIN GUSTAFSON: Can I start discussion, hopefully not close discussion. But I think you in the blood industry, and we who regulate you are in a difficult position, because blood is

viewed different from other drugs and medical devices, and it hasn't been so long ago that it was either the President or the Vice President as part of the Reinventing Government said break down the barriers that prevent you from listening to your regulated industry.

It all sounded very, very good, but then when it came into practice, for blood it's, oh, no, that's an illegal advisory committee; it's in violation of the Administrative Procedures Act, you know, on and on and on and on, and you're being too friendly with industry.

I think, you know, the complaint that often happens with CBER or has since the Eighties is that, you know, we are in bed with industry; so, therefore, we cannot be effective regulators.

So we have had to be extremely careful. I mean more than the drug and device industry. HIMA, who represents Health Industry Manufacturers Association represents the device industry. They will come to CBER, and they will say why can't you be more like CDRH; we work with them all the time, we work with them in developing guidance documents.

Of course, we look to CDRH and we say, how do you do that. I think that there is a mechanism, even with GGP, for having industry input at the very beginning, but still have the guidances go through the

internal review process within the FDA and also out for public comment according to the GGP SOP that we function under.

The Coalition for Regulatory Reform was established to be a mechanism for dealing with FDA of a group to represent the entire industry, and we have worked with them somewhat with the 601.12.

Now, you know, I will share with you that when it got out in public that we had met with the CFRR, questions came from the Hill, why did you meet with them, what was the topic of your discussion, and are you in bed with industry again.

So we have to be careful, but I think, you know, from the President on down, there is a directive to communicate with the regulated industry to bring them into some of the standard setting.

You are the ones who are out there doing the work. So you are the ones who really should know what the standards should be and, yes, we do still plan to regulate you, and we have the final say, and it's not that you would be developing standards and then saying, okay, FDA, here it is, take it as it is; but it would be having a mechanism to have input, hopefully earlier than before a draft guidance goes out.

I think all of you feel -- and you know, honestly, so many of our guidances that have gone out

have been considered to have public health implications. So we have asked that they be implemented immediately during the comment period.

So from your standpoint, it's kind of a done deal before it gets published as a draft. For these two pilot areas that we are developing right now, we want you to know that it's not a done deal, by any means, and we don't want you to implement it when it's published as a draft. We want the comments.

Developing these two pilots was part of the overall blood action plan, and that plan did not have built in an industry communication component early on. However, that's not to say for additional pilots that we cannot devise a mechanism to have, you know, groups work with FDA in developing the initial guidance, and then having the guidance go through GGP with a public comment period, and with FDA having the final say-so.

So I think it's input. I don't think it's conflict of interest. I think it's the ability to listen to you at the formative stages of these pilots and developing the guidance document and the licensing criteria.

Your comments?

MS. HOPPE: Yeah. I think it's completely possible for industry to participate. We consider the highest standards possible to be our competitive edge,

but we believe we can meet higher standards better than the rest of the industry in general.

So there's no objection to having high standards. I think part of what is a little bit disturbing, though, is some of the information in the current proposal, for example, seems to reflect exactly what was there in the 1980 guidance. I don't think it's kept pace with what's gone on in the industry.

I think, to some extent, it reflects insufficient knowledge of what the industry really is and does, and I think one particular point that I would take issue with is the sort of location by location idea being applied to a red cell immunization program that's run off centrally developed SOPs.

I can see with blood irradiation equipment that the facility by facility issue is real, but the fact is, even though the individual physician on site makes a big difference, he can change any day of the week. He can change the day after you issue the license.

At that point, the companies reevaluate, approve the paperwork, and the FDA basically doesn't have even something in their file that indicates who the new person is. So making people wait many months so that you can come out and personally meet the physician who may change tomorrow doesn't make a lot

of sense, doesn't add a lot of value.

I would like us to see us put all of this effort into something that adds more value, and I think it's a good initiative. I don't think eliminating the review process on this particular program gives us as much return for the effort as we might in some other ways.

CAPTAIN GUSTAFSON: Okay. So, hopefully, you and some of the other members of the industry will give us some ideas on a pilot that might be more beneficial.

MODERATOR CONLEY: Essentially, if I hear you right, Ann, you're saying that the added value in the approval process of visiting the actual location is not a significant one, that instead you think there are alternative ways that you can demonstrate physician performance at the actual location where immunizations occur.

MS. HOPPE: I think, if you really want to add value to that process, having some genuine standards for the physician and for what he must know would be useful. I think, to a large extent, even though CBER personnel are involved, there is difference form one inspector to the next, and I'm not complaining about people being too difficult, but I do think sometimes I see people that are too easy.

Well, I don't want to see my competitors

get licensed with an easier inspection than I had, and it comes down to that, that I'd like to see a uniform standard. I'd like to see the right questions being asked. I'd like to be sure that every facility meets the same standard.

I think physicians are important, but I don't think the pre-license inspection process really does much to ensure that.

MODERATOR CONLEY: Ann, before you leave, I'd like to hear you expand on your comment -- concerns about ease of licensure, especially for competitors, in the concept -- is the concept of self-certification viable? Do you think it increases the risk of -- if we use a self-certification approach for certain products, that you may have competitors that get by easier than the standard you set for yourself?

MS. HOPPE: No, because I think what's being missed here is the fact that, for the most part, red cell immunization protocols are being run by major companies, and there's already a sufficient amount of control and a sufficient experience with the license submission process that sending you another bundle of paper just means you run the Xerox machine again.

I mean, it really isn't changing industry's burden very much to say we're going to waive the review. In essence, it's already waived, because it's a repetitive process with additional

sites.

MODERATOR CONLEY: Okay.

MS. HOPPE: But you've got an SOP in place. So I don't think that part of it changes very much.

DR. LEE: Those are excellent points, and we thank you. One thing to keep in mind, though, is to decide whether or not this whole idea of self-certification is a drastic change from the traditional ways of doing things.

If you feel that the self-certification is not that different, not a major change from the way we have been regulating the blood industry for years, that it's not such a significant departure from that, then I think we can encompass more drastic measures such as the ones you propose. However, if your answer to that question is, no, this is a major change, this is a major departure from the way the blood industry has been regulated for years, then I think the approach is to make very small steps, to make small incremental steps and look around as you go.

The two pilots that's proposed today represent just that. They don't purport to be the answers to streamlining in one step. What we propose is simply the step one of a number of steps. We don't know how many steps it will be, but I think starting cautiously rather than jumping to the fruit is a

reasonable approach at this point.

It's certainly better than not doing anything, I think, in terms of streamline initiatives. At least, people are thinking about it, talking about it, and we're moving forward. Once you've begun the process, I think you're 100 percent better off than not having begun the process, and to what degree you've begun the process is less important than the fact that you've begun the process, in the first place.

That's all I have to comment as a response to that, but those are excellent points, and we wrestle with that question internally.

MODERATOR CONLEY: Jan, please identify yourself, and your comments.

MS. SIGMON: Jan Sigmon from the Department of the Navy.

I want to say a couple of things. One is that I see this forum as a really an interesting and innovative way of addressing some of the issues that may have been brought up to you last year in December with your first workshop at NIH that you brought up on the BLA and the changes that were coming.

I know that that was an interesting session. I'm part of an organization that's actually small and yet has a big voice sometimes, and sometimes we have a very little voice; and I don't pretend to

speak for the entire Department of Defense. Please understand that right now. This is Sigmon talking. So I should have just said Sigmon.

I'm really confused, because I'm hearing that you're -- First of all, I guess this idea that you're doing a proposal for a small tool that would help you and maybe help us do things faster. It 's a tool in a basket of other options to do the same thing.

I don't have a problem with that. I think it's great when you come up again with a new tool or a new possibility. The problem that I have is severalfold. One is that where I'm sitting here and automatically in my head developing this idea, oh, great, if we can do this, maybe I can get platelets pheresed, you know, supplement to that quicker. I can do this quicker. I can do that quicker.

Then I'm hearing that if I self-certify myself and you come out on a couple of occasions and see that my supplement is good and that I'm doing well, can I then continue to maybe go through this same avenue to get other supplements, and at the same time then I'm told no, because on some of those things we have to see the documentation first. We have to see the validation first. We have to do this other first, because we can't trust you to give us the information, even though you may have already self-

certified in some other areas.

So, Dr. Lee, you did rain on my parade a little bit there. I'm saying that, you know, again, self-certification is a very thing. I think that all of us have gone through a tremendous rise in standardization and trying to do better with the QA and the documents that came out in '83 and '85, but I also am concerned because last year at that same meeting I also heard the Coalition make a statement that I was just horrified at as a part of -- I think we were one. The Department of Defense was one of five people in that -- or five groups or six groups in that organization.

A statement was made about self-certification and doing it, and what difference was it making. I don't want to misquote, but there was a real slight that was put on the FDA in that, and I was very appalled at that statement that was made, and it reflected on, you know, paying inspectors to come in.

I think that that's one of the things where I appreciate a totally unbiased perspective from the regulatory industry coming into my association to see am I complying according to what you would like for me to comply with. That doesn't bother me in the least.

I open my doors and say come anytime, even though sometimes my doors are squeaky. They're there,

but I do know I'm going to get -- Maybe it's going to be a little bit -- some inspectors are going to be a little bit more picky than others, but at least I'm going to get a perspective that somebody totally unrelated -- I didn't have to pay them -- is coming here and has given me this information; and yes, in fact, I need to comply with it. I don't have a problem with that, again, because of public safety.

You know, I'm listening. I've seen B-PAC. I've seen all this other stuff, and I keep thinking the one people that's not being very well heard here are the small centers, the transfusion services who don't have the money to go out and to buy prisms to do their testing.

They're going to have to go to bigger associations to get their testing done, because they're saying, you know, if we don't have that kind of money, does that mean that we can't do it as well if we have the instruments and the devices. But the leading industry has a lot more money to go out there and tell you guys what to do and get you to move in their interest rather than the little guys.

I mean, ISBT-128 is one of those things also. It's like we've implemented a great deal of high tech stuff the last couple of years, and there are some people out there that are left behind, because they don't have the money, and they don't have

the -- They don't have the ability under a consent decree to focus on it to bring themselves up to a standard that now is higher than the little guy can do.

So my question is -- to all of you, as you do this, it's like we're putting a lot of stuff in the same -- in the bucket, self-certification and looking at individuals who say, yes, we can self-certify; but they have money to do this, and they have more time and effort to do it maybe.

Then at the same time, some of us are trying to work to self-certify, and yet our data is not accepted, you know, in the same level. So I'm just saying that all of this is together. I'm very confused as to what is good and what is bad. I'm confused as to does the industry speak for me? I don't think so, actually, because they are moving a higher level of SD plasma and PCR testing.

Again, these are leading the little centers out to where they can't -- They have to go out and send for their stuff to be done by somebody else. They lose control over it, and look again, what happened to one center that supplies a lot of reference testing for somebody. Now the entire country is going out trying to recall and do look-backs for five or six years.

So my question is what are we doing to all

of us out there?

Finally, and I do mean this finally -- I'm going to sit down -- is that with BPAC and everything else, I've sat through those, and we're letting the public tell us what to do.

We're -- They're telling us what to do without scientific and medical evidence. I heard -- You know, you're put in a position where you have to listen, but isn't there any kind of statement that the FDA can come back to say that -- The blood industry has improved. The incidence of transfusion transmitted disease is down a great down over the last 15 years.

Isn't there anything we can say to make a statement that says we are getting the best that we have and we can, and we continuing to improve? However, the continued litigation against the blood industry over silly things like can we control whether CJD is going to pop up in the blood 30 years from now -- we can't do that, but we can give somebody an improved life for the next year for transfusing them now.

Why can't there be somebody that will stand up and say we're going to save your life today with this blood transfusion; if five years from now you come down with a TTD, then -- you know, again if it's because we neglected to do something, that's

okay; but it was the best thing for you at that point in time, and it gave you five or six extra years.

Can we ever say that to them? Why do we have to continue to try to raise our standard higher and we omit Chagas' disease, which is a very important disease in blood transfusion and could possibly cause problems, and we're looking for CJD 30 years from now.

I'm sitting down now.

MODERATOR CONLEY: Jan, don't leave the mike, because I want to recap, and I want you to tell me if I'm got things wrong, because there was a lot said there, and I'd like to kind of bullet point it for the sake of discussion.

I heard you say that there's a lot that FDA does in oversight that you actually value in the practice that you do as a manufacturer of blood and blood products.

MS. SIGMON: Absolutely.

MODERATOR CONLEY: I heard you also express some concerns that are beyond the regulatory purview of the FDA, concerns about the way the industry is going and whether the small guy is going to be able to survive in this any longer or not, and I'm not sure that that's the FDA's role.

I know it's not the FDA's role to be a champion for the safety of blood products in particular other than to demonstrate that we're

fulfilling our role as a regulator. If you want somebody to be able to cheer the blood industry on, I don't think that's FDA's role, and I'm sure Mary will be able to comment even better on that.

Yes, we're driven by the public, and we're driven by the legislature as to what are the key issues and critical issues. Is full safety of blood possible? This has been debated endlessly, and what are the key issues? That's very difficult, and again other than to assure the public safety as is dictated by the law and the legislature and the public, our hands are kind of tied.

I'm sure Mary wants to comment, too.

CAPTAIN GUSTAFSON: And why are you sure that Mary wants to comment?

You know, Jan, you have very good points, and you're kind of preaching to the choir, I think. Is blood banking policy science based right now? I think the answer is no. You know, science enters in, but we're still ruled a great deal by the public perceptions from the Eighties, and I think, you know, we took a hard blow, and it's going to be crawling back slowly.

You know, when I read in the paper about bad drug reactions on a drug that hasn't been on the market for very long, it's like, oh, yeah, you know, that's -- it might be mentioned once on the news.

Might not even be mentioned on the news.

I think, gee, you know, if that had been blood from a blood bank, this would be discussed for weeks and weeks on end, and we would have all these things, what are you doing, you know.

So I think we are still reeling, and I think even the book that you told me about, the one that's out -- can't remember the author now, but it starts out by saying blood is different; it has a different meaning than other therapeutic products, you know, just historically.

I think your points are very well taken. You know, what I heard from you is concern that the -- by industry input that it will be the large players that will rule rather than, you know, some of the individual transfusion services that maybe don't have the money to move quite as fast.

MS. SIGMON: And if I can add one more thing that goes along with that, what I would like to say again is that everything I have to say is actually I applaud the FDA. I applaud the FDA's looking and what Elizabeth said about the problem is in some of these plasma centers is the doctors.

I don't know about the plasma centers. I've never worked in one, but I do know about blood banks, and I know that many times the medical directors -- they decide to waive a standard here or

there, just because this donor is needed at this point.

I think a lot of times they do not know what's really going on, and I think that, to say that -- I mean, I can see where that's a big problem, and I applaud your unwillingness to let it go and to go on and to certify centers with thinking that the medical director is going to be fine; because I think that that's a big problem in a lot of places.

Again, I have a lot of oversight over a lot of different centers and have had a lot of experience in my career at seeing different centers, and a lot of times the doctors don't know, and they don't really take a vested interest in what's going on in the donor room where a lot of things can come down.

So I'm just saying I do applaud most of your efforts. I do have a problem with the industry speaking for everybody, because I think that they don't.

MODERATOR CONLEY: If we were going to seek industry input for the development of future monographs, do you have an opinion on how FDA should solicit that input and --

MS. SIGMON: I can only tell you that I have 24 centers, and we can't do standardized SOPs, because, no matter what, doing things by committee is very difficult, and everybody in the committee has a

hard time with accepting one little glitch there or one little glitch there.

So I wish you luck. If you can do that and get those monographs to where everybody agrees with them, then you're doing better than I can do with the Navy, and I really better get down at this point.

MODERATOR CONLEY: Okay. The next person from the floor, please.

MS. JETT: I'm Betsy Jett from NIH. I wanted to add one comment to Jan's about how industry standards become standards and tell you a story about my last FDA inspection. I'm going to preface it by saying that I, too, appreciate the inspection process, and I always learn something new.

In the last one we had several discussions about what I considered trivial points, and they had to do with the level of documentation under CGMPs and, you know, do you have to record the lot number of this or that.

In the end, the argument was, well, everybody else is doing it. So you need to do it, too. That's industry standard. I thought of calling around every other place and seeing if that was true, but I didn't.

So what ends up happening is, you know, with everybody under a consent decree, and we are applying these rigorous documentation requirements, I

think, artificially -- you know, without a good, valid reason for it except that, well, you know, the inspector said. It's easier to do it than to argue about it.

I would ask that, when something new like that comes along and you ask us to document something under CGMPs, the burden of proof that it's effective and will make it a safer environment should be on you and not on us, because if we weren't having a problem to begin with, adding a new level of documentation is potentially less safe, because it distracts you from what you're doing. But anyway, that wasn't what I got up for.

What I wanted to say was to make the self-certification viable, I think we have to have viable guidance documents. Where the irradiation one looks okay, just from skimming it, the last one I remember trying to help write an SOP from is the HCB lookback, and that was -- I mean, I think that I have some pretty sophisticated people at my facility, and it was tough going through and trying to figure out what the expectations were on that document.

So I have some suggestions. The first is to heed Al Gore's directive for plain English documents. I would suggest, before you print the draft, run it by somebody in the office, the housekeeping staff, and see if they can understand

what you wrote. Ask somebody to review it that wasn't really involved in creating the document, because it really is hard to implement something that you don't understand.

I just want to say that I think, you know, a noncompliance is not intentional in most facilities. It's because we don't really understand what you're asking us to do.

The second thing would be to allow more easy dialogue in the pre-submission phase. If you want us to be able to self-certify, we have to understand what you want from us. So it won't be successful unless we understand what your expectations are.

To do that, maybe you could empower your employees to talk on the telephone more freely, because I find that when I call on the phone, people are -- and you just said it a few minutes ago. You're afraid to make a statement, because somebody is going to quote you the next day.

So we don't get the information that we need, and a casual conversation, if we promise not to use your name, I think, would be appropriate.

MODERATOR CONLEY: If I could interject at that point, I think you're on the mark when you discuss guidances that have been published that are difficult to read and interpret.

I believe that most of the consumer safety officers in our group have no problem making a statement of fact on a policy that they understand. It's when they're being asked to interpret something that the agency has not taken a clear stand on that you will probably find them less willing to make such a statement.

Basically, we share the same problem. I know Judy and I at a workshop at AABB this year heard from many participants how helpful their consumer safety officers are and how quick they are to respond when they can. Hopefully, that's the issue, and what it really ties into is your first point.

Have the things been published so that they're clear for us, so that we can give you a clear answer. But I don't want to cut you off. You had another point.

MS. JETT: Yes. The next part, and still talking about the documents themselves, is it may be useful after you've published the document to validate it, as we have to validate our SOPs, by using the 483s and the things that appear there and assume that maybe that item is on the 483 because people didn't understand the document.

So use the information from the inspection to improve the guidance document.

Then finally, I would like to see you

develop a knowledge base on the Web where, as people -- you know, people interpret regulations and guidance documents every day through the inspection process through licensing or whatever other mechanism you do it, and it would really be helpful to be able to share the experience and the knowledge of other people by publishing that in a knowledge based system on the Web, so that your staff could use it and we in industry could use it to help understand how to interpret and how to implement.

That's it.

CAPTAIN GUSTAFSON: Betsy, could I ask you a question? Do you mean perhaps a Q&A format on the Web along with the guidance that maybe would clarify areas that seem to be in question?

MS. JETT: You know, there's a lot of different mechanisms for a knowledge base. That's one of them, and there's others like, you know, if you have some sophisticated computer people there, developing sort of an intelligence base where you could -- you can go see a subject and dig down and find, you know, how something has been interpreted or what applies here and there and how you can apply it.

You know, that's a computer technology kind of question that I'm not an expert in, but I know I've seen, you know, in other FDA sites things like that starting to develop. I couldn't tell you where

they are, but I've seen them and said, oh, I wish CBER would do that, too.

Part of it is questions and answers, but it would also be how -- you know, like -- I don't know -- in the legal profession, you know, how a case was decided and what was the rationale behind that case. Those are published.

MODERATOR CONLEY: Good comments. Thank you. Ann?

MS. HOPPE: Is it completely out of the question to think about self-certification to an existing approved SOP versus a single monograph that everyone has to do the same thing?

I mean, what disturbs me about it is that none of it seems to be performance based in terms of successful programs, that I may have a protocol that's slightly different than yours, but if I'm getting a 90 percent success rate and other people have 50 percent, maybe it would be more valuable to approve my program rather than saying, you know, I have to give up the exceptions I have approved if I want to use this standard process.

MODERATOR CONLEY: Is there a reason why you could not approach exactly what you're asking for under a comparability protocol?

MS. HOPPE: No, but the subject today is this process.

MODERATOR CONLEY: Yes.

MS. HOPPE: And it would be nice if there were a process like this we could use short of having to put the resources into developing comparability protocols. It seems to me that it would make more sense, and things like, you know, the admonition to test for alloantibodies -- sure, we test for alloantibodies.

You're not commercially viable if you don't produce products that are relatively free of extra antibodies. But again, if I have a performance history of .1 percent production of unwanted antibodies and other people got 10 percent, maybe my differences are sufficiently good that I should be allowed to keep doing them and still use this process.

I think -- You know, again this is sort of superficial in a way, rather than doing something that's really going to add value and be something we can use. I mean, we're the largest red cell immunizers probably in the world, and I can tell you I'm not going to use your process the way it's written.

MODERATOR CONLEY: I think standardized processes -- it's a relatively small step for us to accept applications self-certified on an industry standard accepted SOP monograph, but to make the leap that everyone will be able to write their own SOPs

that they will self-certify under -- that's a leap. I would not be ready to advocate that yet.

I don't know where we'll end up in a few years.

DR. LEE: I appreciate your comments about the scope of applicability and usefulness as currently defined today, but once again, this is only step one. I think what you're envisioning is step 10 of the process.

Once we get there, we may very well wind up embracing some of the ideas that you just expressed, provided that we receive from you appropriate rationale and justification and demonstration that that is indeed the case, and that the case for you is also generalizable to other centers, not just in your management but under other people's management.

Then we will certainly welcome the -- embrace that idea. However, I think there is a long bridge between that end goal, which we hope to eventually arrive, and where we are today. That's based on inspectional experience.

To make a single step jump would be premature, and we're taking cautious steps. So I'm afraid that, if you're not going to use our process today, that's certainly your option, and that's simply -- that's the end of that.

I'm regretful that it's not useful for you. However, we hope to invite you to comment, as you just did, perhaps with a little bit more substantiation behind your arguments, so that it's useful in expanding the pilot program, as once again we are only at the rudimentary stages, and we're not clear exactly how to take the next step.

We have taken just the first step, and your comments will be very welcome in taking the next steps towards some vision that you already have in making the process more efficient.

MODERATOR CONLEY: Let's take a comment form the back, and then we'll come up to you, Kay.

MS. LeBEAU-LAIRD: All right. I'd like to address that question. Is the concept of self-certification viable? First of all, is that term correct, self-certification? I just fail to see how we are certifying ourselves.

To me, the difference in this paradigm is the location of the documents. Before, we would send in SOPs and QC documents, and you would look at them at CBER. Now we're going to be sending in just the submission, and then you will come out, and you will look at our SOPs and our QC documents.

So would you explain to me how this could be called self-certification? I feel like dumb and dumber here.

MODERATOR CONLEY: I'll try first. We are in a validation stage of a process. So during the pilot an on-site certification will be used. If it is demonstrated that you may self-certify in these instances, an on-site inspection may cease to be a part of the self-certification.

We are validating an approach which -- You've all been through validations now. What the future holds will depend on the performance we find when we go out and look during the pilot. It may well be -- and, you know, what's the future hold?

My own bias with interest in QA is that we would sample a designated subset in some kind of a directed audit in the future, assuming that the first initial validation is good.

Somebody want to add to that?

CAPTAIN GUSTAFSON: No. I think you did fine. That's exactly -- I mean, we recognize that, as the pilots are designed right now, that we are just moving the review to the inspection rather than really accepting at face value your self-certification. But we feel that we need to do that in order to see whether this is really viable.

There are issues -- You know, one basic non-compliance, but as Betsy just mentioned, there may be problems with the guidance that didn't come through during the comment period even. So we're validating

both your compliance and our own guidances.

MS. LeBEAU-LAIRD: I see. So if you go out and say 95 percent of the facilities in the model, in the project, look fine, then is what I'm hearing that maybe you won't be going out to do inspections after that for these license applications?

CAPTAIN GUSTAFSON: Yes. That is a possibility. That's what under consideration, that if the pilot is so successful and the industry shows that they are able to certify to a guidance and follow it, then I think we would license without the pre-approval inspection.

MS. LeBEAU-LAIRD: All right. Thank you.

MODERATOR CONLEY: Give me some feedback on that before you leave the mike. You used 95 percent, I'm sure, off the top of your head. If we had 12 people submit to participate in the irradiated pilot and 11 of them were certified immediately following inspection, and the 12th was egregiously horrible -- people weren't trained, products were being irradiated at 3500 Centigrade, abandoned twice if they forgot to put the sticker on, people weren't trained -- is that a successful system?

What do you think we should look for in order to judge whether we have a successful pilot?

MS. LeBEAU-LAIRD: I'd have to think about that.

MODERATOR CONLEY: Okay. Think about that, and write in.

MS. LeBEAU-LAIRD: That's what we have been thinking about.

DR. LEE: Well, obviously, five percent is not always five percent. I mean, one out of 12 is not the same thing as ten out of 120. Each carries a different weight of being able to serve as in a probability model.

So I think you have to think about confidence intervals. First of all, five percent is too high, to begin with. I mean, if you are proposing .1 percent, perhaps we can consider that. If that .1 percent is validated enough based on statistical analysis that it's actually .1 percent, no matter how many such studies you conduct, then perhaps it's acceptable; but then at that point it becomes a judgment issue as to what level of risk you are able to accept and what level you are unwilling to accept. It becomes more of a judgment call.

At some point, with every statistical analysis, there's judgment involved, first of all, what's acceptable and what's not. Then once you have clarified those ideas, then you begin to run numbers and assess the predictability of that particular outcome to other broader situations.

So I think this is why we are in the

initial "Phase I" stage of this -- exploring this new policy, to get an idea, initial idea, of the experience based on which we can perform larger studies which are then geared to actually deriving some numbers that give us numbers about predictability as applicable to other bigger situations.

MODERATOR CONLEY: It's pretty clear to all of us that, if we applied standards comparable to HIV risk and CJD risk, probably nobody would get licensed for anything. Are we science driven anymore? I'm not sure.

Let me just mention in passing, because I see more and more people sneaking out, there is an evaluation form. We very much would appreciate it if you complete that and leave it on the desk outside, as to whether you have found today's meeting useful or not, and thank you for waiting, Kay.

MS. GREGORY: Hi. Kay Gregory from AABB and frequently a spokesperson for CFRR, for those of you who might not know me.

I just want to express my thanks for having the workshop today. I think it's been very useful. We've heard a lot of good information.

In response to this particular question, I think that self-certification is very viable. I would echo some of what Betsy had to say in terms of I think one of the key ingredients is that we all need

to understand what it is we're trying to certify to.

So we need a good guidance document. We need good understanding of what it is we're trying to do. I don't think any of us deliberately don't comply with something. We simply don't understand that it's meant to be interpreted this way or that way or some other way.

You're writing guidance documents. I know it's very difficult. I do a lot of writing, and people write back and say, well, you said, and that wasn't what I intended at all. So trying to write in plain English -- and I think maybe the idea of a checklist wasn't so much the idea that we just want a simple checklist, but maybe a -- or guidance document with bullet points instead of long sentences that I can't figure out what they mean, you know.

So I think that was one possibility for a checklist, is not just a checklist where you go down and check, but where it would really give you what you really intended it to be, if there are limits that you want it to fall within this or that or whatever.

So I think the concept of self-certification is one that we should explore. If I'm hearing things right today, the pilots are really just a beginning step, and you need to have some way to sort of evaluate whether you're going the right direction or not, and I think this may be a way to do

it.

I'm not sure that for the blood side you've chosen the pilot project that will have a lot of interest, but I think you won't find out until you float it and see. I was glad to hear that, if you think there's not enough interest in this one, you would look for something else that you could do on a pilot basis.

So again, I'd like to thank you for having the workshop. I've found it very useful.

MODERATOR CONLEY: Thank you, Kay. How many of you either represent an applicant or know of somebody, another applicant, who would be interested in participating in one of the two pilots we described today? If you both know somebody and you are one, you can do this.

So there's some interest in our relatively small group here today. I see about five hands, I think, and it is not a huge representation.

Cheri?

MS. JENNINGS: Yes. As the concept is being presented on a basic level, I think it's a very good one. When my institution has been unsuccessful in a license application, it has been because we have failed to address some key issues that you think are very important.

When we have been successful on the first

try, it's because someone like Gil, our consumer safety officer -- in other words, Linda Alms -- has said make sure that you address the following items.

So if these are put into the guidance document that we can understand clearly and with the possibility of knowing that our application will be complete within a 90-day period, I know people at my institution particularly would be very favorable to that.

I know there's a lot of work that needs to be done, but the concept as you presented it today to me seems like a sound idea.

MODERATOR CONLEY: Again for our record, that was Cheri Jennings from Gulf Coast.

Please come and use the mike.

MS. VAWTER: My name is Mary Lou Vawter, and I'm with San Diego Bio Health. I have a concern about the self-certification as far as the small guys like myself. We're just a small, little plasma center, but I've been doing red blood cell immunization since '85, and I've worked for some really good people and I've worked with some really bad people.

Unfortunately, the bad people are really bad, and it isn't until somebody comes forward and reports it that something happens. But I'm afraid that bad people might get into this again. You know

what I'm saying?

MODERATOR CONLEY: You mean, and ruin the pilot?

MS. VAWTER: Yes. I mean, who's to say that somebody that has had their license revoked can't use somebody else's name and get back into the industry again and just go back with the same shenanigans that he had before.

It concerns me, because I mean, I've been dealing with the same donors since 1985, and I don't want my donors to be at risk with people that are in it for just the money.

CAPTAIN GUSTAFSON: Are you saying that perhaps this is too risky of an area to pilot?

MS. VAWTER: The red blood cell -- I'm kind of -- I kind of feel that way, but I mean, I know I try my best to be in compliance at all times, but when you have somebody that you once worked for that wasn't and telling you different things that aren't really true -- you know, I mean, I'm afraid other people will get into this and really have no business being in this industry.

DR. LEE: Given the fact that we have the license -- actual pre-licensing inspection retained as one of the review components, and given the fact that we have limited this to the users of qualified cells as supplied by others, do you think that this affords

less public health protection than the current ways of doing things?

MS. VAWTER: Well, that's true. I didn't think of it that way, but who's not to say that he goes -- or somebody can go to someplace that's already licensed and then go ahead and get a red cell? You know, I mean --

DR. LEE: Yes. We have thought about that.

MS. VAWTER: Where there's a will, there's a way.

DR. LEE: I'm glad that you are thinking along the same process that we've already pursued. That's quite correct, but I think those are risks that are already existing, and we hope not to increase risk but just to find some means of improving the process without increasing the risk and, perhaps at the same time as a by-product, maybe increase safety as well.

MS. VAWTER: Okay.

DR. LEE: But the pilot may fail, but then it fails for a good reason, and then we'll be very glad it failed, but then that doesn't mean that the whole program has died. We will simply move to another specific area of regulations.

MODERATOR CONLEY: It's heartening for me to hear some of the industry express some of the same concerns that we have had internally as we try to find

more efficient ways. Unfortunately, we don't regulate just the good guys or we don't have a way of splitting out and regulating just the bad guys. We make a regulation that has to be fairly applied to all and, hopefully, we limit the bad guys in the industry.

Go ahead.

MS. JETT: Yes. A comment on how you might evaluate the program itself. Somebody had mentioned, well, you know, is it going to be -- there's no 483s or no significant ones.

I would say maybe you should compare it to the number of 483s you get using the traditional approach. I can't imagine that there's none under the current program. So why would you think there would be less under the new approach?

MODERATOR CONLEY: Excellent point. Make sure we are at least doing as well or better than we were under the old approach. Very good.

DR. LEE: Well, once again not to rain on the parade, but under the traditional approach, the 483s must be addressed before an approval is released. So is the pilot.

If you -- I mean, that -- Oh, I see what you're saying. Yes. But I guess in terms of accepting the ultimate -- the application in terms of the final approval, it's rendered after all deficiencies have been properly addressed, and we

certainly want to do that under the pilot as well, but how do you declare success of the pilot?

If we always have to -- If we are throwing people out of the pilot because they don't cut mustard at inspection, then that doesn't mean that they can't be licensed. They will be licensed through the traditional means, but the pilot has died.

So I think, of course, we will keep in mind the number of observations cited under the traditional system, but that's going to be way too high. The number that we're aiming for has to be far less than that in order for the pilot to actually be declared a success.

Well, because -- not necessarily it's good or bad, but just because the fact that if the number of observations are high, then we are continuously falling back to the traditional ways of reviewing things, and by definition, the pilot has failed.

Basically, we're trying to arrive at a number which we can -- which gives us confidence that we can move forward to the next stage of the program, that we do not have to fall back on the traditional review, that the initial self-certification is indeed self-certification as we want it, and move forward.

So unless the findings at the inspectional stage of the pilot is only of fairly insignificant public health importance, I think by default the

program, as defined in that area, cannot move forward.

So I think the ultimate number has to be much better than the current inspectional experience under the traditional program.

MS. JETT: Then maybe I'm misunderstanding the intent of the whole program. I thought it was a streamlining thing, not an improved safety program necessarily.

DR. LEE: Well, we endeavor to streamline, but not at the expense of increasing -- not at the expense of safety. Basically, if the pilot program -- If the findings under the pilot forces us to continuously throw people out of the pilot program, then the answer to your question would be, well, the pilot program is not viable.

MS. JETT: Okay. But I just don't see why you would expect a facility to be more successful at implementing guidance in the pilot program than under the traditional process unless you're changing the --

DR. LEE: We don't necessarily expect anything at this point. I mean, if you submit an SOP to us and review it, and we get it to the shape that we want it, then we know it's okay, because we had an input into the process.

MS. JETT: Okay, I see what you're saying.

DR. LEE: But without that -- I mean, we tried to tailor these guidance documents released

under the pilot -- we try to tailor them to be very SOP oriented and detailed and specific, not leaving a lot of room for other considerations. It's intentionally written that way so that it can simply be taken as it is and be readily converted into an institution specific SOP.

Whether or not the industry can acceptably do that depends on, as you said, the clarity of the document and the willingness to comply. We believe that, in general, people are willing to comply, but often are not able to comprehend exactly what should be in their institution specific SOP, and the challenge is on us to make sure that these guidance documents are written clearly.

Part of the good guidance practice provision is to allow your input which, among other things, will add clarity to the document.

MS. JETT: Would the specifics contained in the guidance document become de facto standards outside of the pilot program?

DR. LEE: Well, that's moving on to a broader question. That may very well be the case, but that's not our intent. Our intent was to provide a mechanism where -- which represents the majority of -- the bulk of the potential applicants.

We want to find out the most common ways of doing things, and we want to convert that into a

system that readily lends itself to "self-certification" to previously written guidance documents. But that's not to discourage other people from proposing more creative, better, more efficient ways of doing things. However, we can't just do that. Those have to be evaluated.

Under the spirit of the pilot program, once you begin to evaluate, you fall down. As it's defined today, I think we want to concentrate on the fact that we are -- at least for the initial stage, the purpose is to obviate detailed review after receiving submission but be able to move right into the inspection.

So by default, it may -- The industry forces may be such that what you just said might wind up being the outcome, but that's sort of beyond the scope of what we can control.

MODERATOR CONLEY: I think our guidance documents, as we publish them now, do become de facto standards. They do not carry the weight of law nor the weight of regulation, but in that the industry complies with them generally, they do become good manufacturing practices.

So more difficult to defend in a court of law if FDA pursued an action against a licensed manufacturer, but still very doable, because they do become de facto standards.

So I don't think these will be any different, but we have to recognize what they are right now and that we've tried to remove a lot of the variables.

Things that you might have been able to successfully defend under an earlier guidance document, if you're going to pursue it under a pilot study, what you're saying is I'm doing it exactly that way so that I can have an expedited review. So that's the difference between the two.

You may still apply through traditional prior approval supplement approach, if you want to do something a little bit differently, if you want to irradiate at 3000 rather than 250 Centigrade; but if you're going to participate in the pilot, then we've simplified it. We've made it straightforward, but we have not tied the hands of manufacturers on how they do things.

MS. JETT: Just make that clear to everybody. I mean, you know, include that in the title of the document, because I think otherwise there will be confusion about what's the requirements for a product versus the requirements to participate in the pilot.

DR. LEE: Yes. Actually, we have tried to incorporate into the guidance title by making sure to include the word pilot.

MS. JETT: Oh, okay.

DR. LEE: I appreciate your points.

MODERATOR CONLEY: I put the next couple of questions up, which are really on technical issues, so that people can -- if you have any questions about the technical or scientific basis in the documents, we can come to that. But Steve was already up and has a comment.

MR. KASSAPIAN: Steve Kassapian from the American Red Cross.

Your previous slide, those are the ones I'm addressing. I believe that this is a significant change, and I believe it is viable; but it's not only viable. I think it's necessary, and I don't see it at all as a conflict of interest.

I think that industry can help in the development of these guidances. I think that in the long run the industry is closer to the manufacturing process, and in many cases they would be more strengthened.

So that's why I don't see a conflict of interest. I also see that we would be able to get improved products to market faster, and that's again -- there's no conflict of interest here.

So it is definitely viable. It is necessary, and we should do it. Having said that, I just want to step back one, because I want to say I

like this concept, but I also like the concept of the BLA and the changes to 601.

I think the problem with both of those is how we implement this process. I think this can prove Mary's point, that we're not in bed together, because even though they get input from industry, they don't always necessarily -- you don't always necessarily implement it the same way or exactly in the fashion we would want, and that's understandable. But we're going to give you our two cents anyway. I think implementation of this will be something that we can debate as well.

You wanted some areas of interest for pilots. Somebody already mentioned leuko-reduction. I would absolutely agree.

I would also mention platelet pheresis. This isn't the first time I would mention platelet pheresis. It won't be the last.

Here's one that I don't know that you've thought about and, from my organization, it would be very helpful -- changes to SOPs in the big six categories. That would be donor suitability, high risk, etcetera.

I think that would fit in nicely to this concept, because here you're giving us -- we're saying we're certifying that our SOPs, our changes to the SOPs, address your concerns, and we have them.

In fact, if you wanted to do a pre-license inspection, which I don't think would be necessary, you would come in, and you would look at the SOPs more effectively. You would look at how the SOPs actually work in the real world.

So I would think I would like to see -- I say I think. I would like to see this type of thing for SOPs, just as a separate part -- you know, changes to SOPs.

I think the question -- you asked the question also, how much detail should we put in these guidances. Somebody asked that one. I think in that case you would want to put in the concepts as opposed to the details.

The only details you would really want would be the specific ones that would be required, such as, say, 2500 Centigrade or the specific details that are absolutely necessary set points or whatever. But by and large, I think that my comment is that this is absolutely doable, and we should move forward with it.

As somebody else mentioned, this is only one tool. You can use this for something else. You could use a comparability protocol for something else. This may not fit for what somebody else was discussing, but there's another tool to use.

So the more tools you can give us, the

happier I'm going to be. Thanks.

MODERATOR CONLEY: Good. Thank you for your comments, Steve.

Any -- Express any concerns or questions about scientific or technical issues in either of the two guidance documents? Perhaps this may be an issue that you would rather go home and put your data together and respond in writing.

We really talked a little bit already about what criteria should be used to evaluate the self-certification pilot, and got some good ideas on that. Steve has already kicked off the idea of what next products should be included in the program, and what would be the best way to involve the industry.

We've also heard some comments, too, and especially some comments and some concerns that maybe the representatives in like CFRR may not represent the small guy in blood banks, and maybe -- Good, Kay is going to address that.

MS. GREGORY: I don't pretend that we represent everybody, because we don't hear from everybody. Certainly, if you let us know what your concerns are, we do try to represent especially the small guys, because we're afraid you don't have a voice of the big guys. But if you don't tell us, there is no way that we can represent you either.

So I guess my plea would be to let someone

know what your concerns are. You know, CFRR was specifically designed to try to work on these issues, and we're certainly happy to do so. We're certainly happy to let somebody else work on it for a while as well, but we can only represent what we know about.

Frankly, we have trouble getting industry input sometimes. So I know most of you here probably are the ones who respond anyway, but if you can take the message back home that not only does FDA want to know what you think, but industry, AABB, the CFRR -- we all want to know what you think as well, so that we can represent you as best we can.

MODERATOR CONLEY: The floor is wide open for anybody on the panel or in the audience.

DR. LEE: Well, I'd just like to make a comment, that I am actually very glad about the size of the audience today, because that allows each one of you to adequately express your concerns and truly come to an understanding of what we presented.

Had we had a much bigger audience, I think the case would be too many cooks in the kitchen, and we wouldn't be able to really reach the level of clarity that we are striving for.

The burden is for all of you to go back and discuss this with your neighbors so that you each individually serve as a spokesperson of the changes to be implemented in the future. So in that way, not

only by giving us your direct feedback, but to sort of serve as indirect spokesperson, I think we can achieve the same goal in a more efficient way.

I guess one more comment about in brainstorming ideas for expansion of the pilot program to include other regulatory areas. I think whether or not it's a suitable candidate may become more clear if you ask the question, self-certification to -- self-certification for adherence to? That's the area that -- the blank that you want to fill in.

If you just think about self-certification, period, that just means that you self-certify, and that you say that you're okay. If you think along those lines, I think you will find yourself thinking in an unclear way. But if you ask yourself, self-certification for my adherence to, and then the question is how do you want to come up with a particular monograph or pilot guidance which spell out the provisions of adherence.

Those are my two final closing comments.

MODERATOR CONLEY: Let me just editorialize a little bit, too. When these documents publish in draft, they are open to public comment from everyone. Every comment that is sent to the FDA is read and considered on its merit in the publishing of the final guidance document.

Often in our busy lives, it's easy to

presume that AABB or CFRR or ABC is already responding on our behalf. In fact, that is the best guard for the small place that feels like they're being left out, is to take time to comment on a guidance documents; and I know how hard pressed everybody is for time, and it's difficult, but that's still the best way to get your comments in to the FDA, because we're not tied to any one manufacturer in asking for support.

I think things are starting to wind down. Closing comments from the panel?

CAPTAIN GUSTAFSON: Well, I'm very, very grateful for the turnout today. I was worried. I was worried both in terms that we didn't have enough material to fill a day, and also that we wouldn't have enough people except for FDA folks to have any discussion.

So I'm very, very pleased that you came. I'm very, very pleased that you participated, and I hope that you will continue and comment on the written draft and send in written comments for us to chew on as well.

We will have the transcript. We plan on studying all of your comments, but you know, keep telling us what you think. I think I've got the idea that the concept is good. You like self-certification, but the devil is in the details, and

whether we have the right pilot, we have the right evaluation criteria are things that, I think, are still under discussion, you know, as we move along.

I think I get the idea that you like the overall concept.

MODERATOR CONLEY: Are there anymore comments? One more comment.

MS. FORD: Kenra Ford, Director of Labs, Inventory Management, the Oklahoma Blood Institute.

I'm very excited about this potentially new pathway. I'd like to strongly recommend that this be considered, and this may be a way to launch off this new opportunity.

For those products where you're already licensed, and you made a major manufacturing change that constitutes re-licensure or new application, for example, donor retested plasma, you've got an apheresis technology and you go to a new version upgrade where it constitutes re-licensure, that may allow you to get the data that you're looking for in a more controlled situation, because you've already got a licensed product in a center that has experience with that process, so that you don't roll in bad outcome data up front that would crater this.

I think this is a great opportunity for a lot of areas, but maybe not all of them.

MODERATOR CONLEY: Very good. Thank you.

Well, thanks to all of you. Thanks for today's participants. I think we all owe each other a big hand.

(APPLAUSE)

MODERATOR CONLEY: Complete your evaluations, and drive safely wherever you need to go tonight.

(Whereupon, the foregoing matter went off the record at 4:12 p.m.)