DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

73RD MEETING

OPEN

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MILLER REPORTING COMPANY, INC.
735 8th Street, S.E.
Washington, D.C. 20003-2802
(202) 546-6666

PARTICIPANTS

Kenrad E. Nelson, M.D., Chairman
Linda A. Smallwood, Ph.D., Executive Secretary

MEMBERS

James R. Allen, M.D.
Mary E. Chamberland, M.D.
Charlotte Cunningham-Rundles, M.D., Ph.D.
Donna DiMichele, M.D.
Michael G. Fitzpatrick, Ph.D.
Harvey G. Klein, M.D.
Judy F. Lew, M.D.
Daniel L. McGee, Ph.D.
Terry V. Rice
Paul J. Schmidt, M.D.
Sherri O. Stuver, Sc.D.

CONSUMER REPRESENTATIVE

Robert J. Fallat, M.D.

NON-VOTING INDUSTRY REPRESENTATIVE

Toby L. Simon, M.D.

TEMPORARY VOTING MEMBERS

Liana Harvath, Ph.D.
Blaine F. Hollinger, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Welcome, Statement of Conflict of Interest

DR. SMALLWOOD: Good morning. Welcome to the 73rd Meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. At this time, for your hearing, I will read the Conflict of Interest Statement that applies to both days' session of this meeting.

The following announcement is made part of the public record to preclude the appearance of a conflict of interest at this meeting. Pursuant to the authority granted under the Committee Charter, the Director of FDA's Center for Biologics Evaluation and Research has appointed Drs. Liana Harvath and Blaine Hollinger as temporary voting members.

Based on the agenda, it has been determined that there are no products being approved at this meeting. To determine if any conflicts of interest existed, the agency reviewed the agenda and all relevant financial interests reported by the meeting participants.

In accordance with Title 18, United States Code 208, Dr. Harvey Klein has been granted a general matters waiver that permits him to

participate fully in the committee discussions. We would like to note for the record that Dr. Toby Simon is participating in this meeting as an industry representative acting on behalf of regulated industry.

With regard to FDA's invited guests, the agency has determined that the services of these guests are essential. There are interests which are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the participants.

For the discussions on the Uniform Donor History Questionnaire, Dr. Joy Fridey is employed by the Blood Bank of San Bernardino and Riverside County, California as Senior Vice President of Medical Affairs. For the discussions of a Warning Label for Hetastarch, Dr. Gary Haynes has an unrelated grant supported by the American Red Cross Plasma Services.

In addition, listed on the agenda are speakers making industry presentations on the Standards for Recovered Plasma. These speakers are employed by industry and, thus, have interest in their employer and other regulated firms.

FDA participants are aware of the need to

exclude themselves from the discussions involving specific products or firms for which they have not been screened for conflict of interest. The exclusion will be noted for the public record. This is in reference to the committee members.

With respect to all other meeting participants, we ask, in the interest of fairness, that you state your name, affiliation and address and any current or previous financial involvement with any firm whose products you wish to comment upon.

At this time, are there any declarations to be made regarding this meeting? Hearing none, I would like to, at this time, introduce to you the members of the Blood Products Advisory Committee.

As I call the names of the members, would you please raise your hand.

The Chairman, Dr. Kenrad Nelson. Dr. James Allen. Dr. Mary Chamberland. Dr. Charlotte Cunningham-Rundles. Dr. Donna DiMichele. Dr. Michael Fitzpatrick. Dr. Harvey Klein. Dr. Raymond Koff. Dr. Judy Lew. Dr. Daniel McGee. Mr. Terry Rice. Dr. Paul Schmidt. Dr. Sherri Stuver. Dr. Robert Fallat. Dr. Toby Simon. Dr. Liana Harvath. Dr. Blaine Hollinger.

I just have a few announcements to make. If you will note on your agenda, there have been some changes made from previous versions of the agenda and I would just like to inform you of those, so you will not be confused.

If you had seen a previous version of the agenda that identified End User Notification, that has been deleted. Also, a presentation on Rapid HIV Tests has been deleted, and we have added to the agenda a presentation on IGIV Supply.

Also, I would like to announce that there will be a workshop sponsored by the FDA on August 7th and 8th on Safety and Efficacy of Methods for Reducing Pathogens in Cellular Blood Products used in Transfusions.

Also, at this meeting, because of a change in our charter, our consumer representative, Dr. Fallat, who was formerly non-voting, will now be voting with the committee.

As far as audiovisual aids, we have a remote mouse, so that those that are using the podium here, that is available for your use, and if you have any problems, please see the audiovideo technician over here to my left. Would you raise your hand, please.

At this time, I will turn the proceedings of the meeting over to the chairman, Dr. Kenrad Nelson.

DR. NELSON: Thank you, Dr. Smallwood, and welcome.

The first topic is a discussion of the current IGIV Supply. Dr. Weinstein.

Current IGIV Supply

DR. WEINSTEIN: Good morning. My name is Mark Weinstein. I am the Director of the Division of Hematology in the Office of Blood at CBER.

[Slide.]

Today, I will give you an update on the status of IGIV distribution in the United States. I will briefly discuss the reasons for a shortage of immune globulin products that started in 1997, the evidence that we had for the shortage at that time, and the actions that FDA took to alleviate the shortage. I will then discuss the current situation and some future directions.

[Slide.]

In November of 1997, FDA became aware of an acute shortage of IGIV. At that time, we did not monitor the distribution of plasma derivatives as we do now. We learned of the shortage through

numerous persistent reports of shortage nationwide from many sources including patient groups, individual patients, hospitals, distributors, and physicians.

FDA contacted manufacturers and distributors and further verified these reports.

Another indication of the shortage was seen by the increase in the cost of products. The cost of products rose dramatically over the next several years.

[Slide.]

This graph shows the shortfall in production that occurred in 1997. It is about down from about 15 percent of what would have been expected had the rate of increase been the same as it had been for the previous four years.

[Slide.]

The principal reason for the reduction in IGIV distribution had to do with compliance issues and problems with industry meeting good manufacturing practices. An additional element was our CJD policy at the time, which called for withdrawal of products made from plasma pools that contained units from individuals recognized post-donation to have had classic CJD.

In addition, the use of product for approved and unapproved uses also increased at a higher than expected rate.

[Slide.]

FDA took a number of actions to alleviate the shortage. These included facilitating increased production and distribution without compromising the safety or efficacy of these products.

These actions included shortening the time of reviewing lot release protocols, expediting the review of license supplements related to IGIV, and streamlining clinical trial design.

Streamlining trial design involved working together with Immune Deficiency Foundation and industry to develop protocols that required fewer patients and shorter time frames while assuring the safety and efficacy of the licensed products.

A Dear Doctor letter was sent out to provide guidance for prioritizing the use of IGIV. The letter indicated what the approved uses of IGIV were and other uses for which there was some or little clinical support.

We required manufacturers to report monthly distribution of plasma derivatives to the

FDA. This helps us to monitor the amount of product on the market and to get a sense of whether a significant increase or decrease of product distribution is occurring.

There was also a change in the CJD policy in 1998, which reduced the number of withdrawals by no longer requiring that product be withdrawn because of a concern with classic CJD. We note, however, that our current policy calls for withdrawals if there is concern about the presence of a variant CJD.

[Slide.]

This graphs shows the yearly increase in IGIV distribution on a yearly basis. So, for example, you have figures here from May of '98 to April of '99 compared to May of 2001 to April of 2002. You can see that there is a steady increase. In fact, there is approximately a 50 percent increase in level of IGIV distribution compared to the '98 figures.

[Slide.]

This graphs shows similar distribution data, but reported on a monthly basis. You can see that there is a general trend upward, but there is considerable monthly heterogeneity variation over

the past year and a half.

Now, it is important to realize that these figures represent only part of the total amount of product that is available for use. There are other reservoirs of product that are in the hands of distributors, in hospital pharmacies, as well as the inventory of manufacturers.

In fact, at the present time, we know of at least 1,000 kilograms of IGIV that are in the hands of distributors, and this additional amount of material acts as a buffer to the monthly variations or swings in distribution from manufacturers.

[Slide.]

An additional indication of the improvement in the supply of IGIV can be seen in this graph of the average cost of IGIV. This average is made up of summing the cost of seven brands of IGIV and producing the average cost.

The cost of IGIV rose dramatically from the level of 1998, which is at $32.73 per gram, to a high of $48.49 per gram in 2001, but as you can see, the price is now declining. The 2003 figure is a fiscal year projection from FFF, a major distributor of immune globulin products to

hospitals.

[Slide.]

To recap, IGIV distribution has increased by 50 percent since 1998. The average price of IGIV has declined from a high of $48.49 in 2001 to a level of $45.74 per gram projected for 2003.

Although there have been variations in monthly distribution levels over the past year and a half, there are significant amounts of IGIV in the distribution pipeline that act as a buffer to variations in release from the manufacturers.

[Slide.]

In summary, the supply of IGIV has improved significantly since 1997. However, importantly, more improvements can be made. We recognize that there is still a high demand for the product, that more product would be desirable, and that competition is good for the industry and for the public. FDA encourages manufacturers to submit applications for new products.

The classification of whether a submission is to be reviewed as a Fast Track priority review or a standard review is a function of assessing the medical need at a particular point in time balanced against other priorities and the limited resources

of the FDA.

We encourage manufacturers to come and talk to us and bring data to help us decide what designation classification a submission should receive.

Thank you for your attention.

DR. NELSON: Thank you, Dr. Weinstein.

Questions? Yes, Harvey.

DR. KLEIN: Do we have any idea about why things are better now, is it that there is more plasma being collected, more fractionation capability, or is it that there are fewer recalls? Do we have any quantitative information, and is there sufficient fractionation capability, so that if the curve of distribution continues to rise, there will still be available fractionation products?

DR. WEINSTEIN: I think that the elements that you mentioned, both further manufacturing capacity, new products coming on-board, increased production by certain manufacturers, importation of materials, these are all reasons why this increase has occurred.

There is always concern about situations where a given company may not be able to produce a

product at a desired rate. We know that these situations can occur at any time. This is still an industry that has relatively few manufacturers involved in it, and if one of those manufacturers does have a problem, there can be a dramatic significant effect on the total availability of immune globulin.

So, these elements, the fragility of this market is something that we are very aware of, but I am reporting on what the data is at the present time. Conditions can change, and our priorities will change with the conditions.

DR. ALLEN: How does the supply track versus the demand or the need, and is there much of the product that gets outdated, or does the FDA not receive information on that?

DR. WEINSTEIN: We don't have direct information about that part of the equation. The hard numbers that we have really are the numbers that we get from our required data collection from manufacturers. We get estimates of availability by making direct inquiries to distributors, finding out how much material is in the pipeline.

We also rely on our good communications with the patient organizations to find out what

their situation is and whether they are reporting that there is lack of material available.

But the idea of an acute shortage, how do we know when an acute shortage occurs here, and those were the items that I pointed out before, this idea of a nationwide surge in reports about product deficiencies, that is what would be called an acute shortage situation.

DR. NELSON: Presumably, a fair amount of the reason for the increase in recent years is off-label use?

DR. WEINSTEIN: A lot of demand for the product is through off-label use.

DR. NELSON: You can't estimate that?

DR. WEINSTEIN: Right, that is very difficult to estimate.

DR. SCHMIDT: Mark, the expiration date that is given, is that from lot release or lot production, and how long is it? That is the first question.

The second question is did you see, on those monthly distribution, did you see any major changes from that Dear Doctor letter that was sent out in terms of prioritizing IGIV in terms of reduction or anything of that nature?

DR. WEINSTEIN: I believe that is a two-year time period for most of the immune globulin products, lot release from the last sterile filtration, I believe. As far as the prioritization or how the product is used, the approved uses in the Dear Doctor letter are still the ones that are currently in effect.

As far as knowing what the off-label uses are, whether there has been an upsurge in that, we simply don't have figures on where the principal uses are now for these other potential uses of product that are not approved.

DR. SCHMIDT: Can the outdated material be reprocessed?

DR. WEINSTEIN: No, the outdated material would-- in fact, there is very little outdated material, that the stuff is gobbled up very quickly.

DR. NELSON: There are a couple of people that wanted to also testify from the Immune Deficiency Foundation.

DR. BARR: Good morning. My name is Richard Barr and I am the chairman of the Board of Trustees of the Immune Deficiency Foundation. I am also an adult patient diagnosed with common

variable immune deficiency.

[Slide.]

This morning, I would like to update this committee on the Foundation's continuing concern regarding the status of the immune globulin supply. Tom Moran, the IDF president, will be assisting me with this task.

Our fundamental perspective is that despite the increasing IGIV supplies over the past several years, our community is still in jeopardy because of the facts we will outline this morning.

IDF, by history, is the national organization dedicated to improving the lives of primary immune-deficient patients through research, education, and advocacy. Primary immune deficiency diseases are inherited disorders in which parts of the body's immune system are missing or do not function properly.

The World Health Organization has identified more than 100 different primary immune deficiency diseases. Approximately, 50,000 Americans suffer from a clinically significant primary immune deficiency disease, 70 percent of these patients use immune globulin intravenous, IGIV, regularly to maintain their health.

For our members, IGIV is literally a life-saving therapy. In 1997, an acute shortage of IGIV in the United States began and resulted in product unavailability and negative health consequences for many patients who require this therapy to maintain their health.

As documented in IDF's 1998 surveys of physicians and patients, which were presented to this committee and other government bodies, we determined that 40 percent of primary immune-deficient patients in the United States got sick, some seriously, as a result of missing or postponing their infusions.

Tom Moran is now going to bring this discussion into the present.

DR. MORAN: Thank you, Richard, and thank you, Mr. Chairman, for having us in. Mark, thank you for your earlier comments.

I am Tom Moran. I am president of the Immune Deficiency Foundation.

In response to the IGIV shortage, as Mark alluded to in his presentation, individual patients and physicians, the Immune Deficiency Foundation, industry, and the FDA all implemented actions to understand the causes of the shortage, reduce its

impact, and eventually increase the available supply of IGIV.

Working with industry, IDF provided emergency distribution of IGIV to patients and their health care providers. Working with the FDA, we encouraged the priority rationing of IGIV within health systems, and based on discussions between FDA scientists and clinical immunologists, the FDA streamlined clinical trial and licensing protocols to encourage new manufacturers to enter the U.S. market and to assist existing manufacturers to develop and license next generation products.

Dr. Barr alluded to the continuing vulnerability in our community despite an increase in IGIV supply over the past several years, which was demonstrated in Dr. Weinstein's testimony.

Our concern, our vulnerability is based on the following four observations or facts.

First, although distribution of IGIV has increased from approximately 15,000 kilos during 1998, to a level approaching 23,000 kilos in 2002, we cannot measure the adequacy of this level in either relative terms or in terms of the health status of our patients. We have no confidence in IGIV distribution estimated prior to PPTA providing

consolidated industry data beginning in 1998, so we do not know where we stand today in relation to pre-shortage levels. Also, the market's appetite for IGIV seems to be insatiable evidenced by the fact that current inventory levels of IGIV equal a three-week supply at the manufacturers' level, despite this increased release of product.

Secondly, distribution of IGIV does not track medical necessity, but rather is determine by distribution channels and market forces, and as Dr. Barr will discuss in a moment, we have good evidence that a substantial percentage of our community is still untreated or undertreated as an artifact or a hangover of the shortage.

Third, the concentration of manufacturing capacity within five companies leaves consumers in a position that manufacturing or compliance issues at a single company could impact 20 percent of the market, which the market is not able to absorb. As a reminder, two of these five companies remain under consent decree for good manufacturing practices, also consolidations among manufacturers, such as the potential merger announced by two of the five companies I have just noted continue to reinforce this trend toward concentration of

resources.

Fourth and finally, other uses for immune globulins, including as a response to specific bioterrorism threats or actions, could have a significant and immediate effect on IGIV supply.

In an effort to minimize the risks associated with this set of circumstances, and based upon our disastrous experience with the IGIV shortage, IDF took the unusual step of recruiting two European manufacturers, and through a related organization, has assisted them in conducting U.S. clinical trials, so as to help to diversify the production capacity available to the U.S. market.

These trials are being conducted under the revised trial guidelines recommended by the FDA in March 2000, and we trust that their licensing applications will be handled expeditiously as promised by the agency in that statement.

We are also consultants to several currently licensed manufacturers in developing next generation products or new routes of administration for immune globulin products.

We recognize that CBER, the Office of Blood, Research and Review, the Division of Hematology are currently operating under extreme

resource constraints, and must balance the interests of primary immune-deficient patients with alpha-1 antitrypsin deficiency, hemophilia, and many other at-risk populations. We are all dependent on FDA to wisely allocate its limited staff resources.

At IDF, we have the responsibility to inform this committee and the agency about the circumstances facing our community.

To close this presentation, Dr. Barr will provide you the results of a survey of IGIV users in our community completed this past January.

DR. BARR: Thank you, Tom.

As Tom stated, our community feels continued jeopardy based on the volatility of the marketplace, concentration of production capacity within the plasma derivative industry, and unplanned contingencies.

Common sense and experience instruct us that while specific problems in IGIV supply are not predictable, they are inevitable under the present circumstances. The root concern for our community is not market economics or competitive diversity, it is a concern for the health and well-being of our constituents.

In this context, we have troubling evidence that suggests significant undertreatment is occurring in our community as a result of the shortage, and that current distribution levels have yet to remedy this problem.

If I could have Slide 1 and 2.

[Slide.]

The IDF recently conducted a follow-up review of the primary immune-deficient patient population. The results of this study point to a significant amount of undertreatment for primary immune-deficient patients, especially as it relates to IGIV supply.

[Slide.]

The most disturbing finding of this study was that 16 percent of the patients who were on IGIV therapy in 1996 were no longer using it in 2001, but were still alive and still affected by a primary immune deficiency disease.

[Slide.]

Another fact leading to a concern for undertreatment is that 11 percent of the patients reported that they receive IGIV infusions every five weeks or less often. Because the recommended dosing frequency is every three or four weeks at a

minimum, in view of the half-life of the product, the IDF is concerned that a less frequent schedule may place these patients at increased risk for infection.

There are many possible explanations for this finding including that providers stop trying to find a stable IGIV supply and abandon this treatment in frustration, or that managed care settings, such as infusion sites and hospitals, abandoned or severely restricted access to this therapy, and have not moved back to appropriate treatment regimens.

Regardless of the cause, the fact remains that our patients are still not realizing the benefits of a sufficient IGIV supply.

In closing, IDF remains concerned with IGIV availability despite the positive direction that the distribution data show.

The volatility in the market and the concentration of manufacturing capacity, combined with our data that a significant number of primary immune-deficient patients are undertreated, leaves our community with a supply that is inadequate to have filtered down to all primary immune-deficient patients and a situation that leaves us vulnerable

to an unpredictable, but inevitable supply disruption.

Our intention is that by keeping this issue in the forefront, we can take actions now that will mitigate consequences of such an event.

We thank the committee for your attention and we would be happy to answer any questions.

DR. NELSON: Thank you, Dr. Barr.

DR. SCHMIDT: Has anybody shown any interest in studying the 16 percent who discontinued therapy--that would be about 50 people--to see what difference it made in their lives if they were no longer getting the material?

DR. MORAN: Fifty of the sample of 300, yes. This survey was conducted in November, December, and we just interpreted the data in January. The next step is to follow up and to get exactly what you are talking about.

Yes, Mary.

DR. CHAMBERLAND: Sort of a companion question. Do you have plans to try to conduct a survey of providers to get their perspective? This is a survey of patients only as I understood it, and I think in the past, you have also surveyed providers.

DR. MORAN: Yes. We are, as an organization, extremely concerned with what appears to be patterns in treatment that on the surface seem to be not at adequate levels, and the answer to your question is yes, and the same follow-up effort with respect to going to patients will also be following up with providers.

I think one of the issues might be there was, during the shortage, a tendency, particularly among managed care settings, to move, say, infusions from three to four weeks or four to six weeks, and clearly, if there hasn't been a disastrous health outcome, there may be a tendency to stay at that level since for the people that are footing the bill, they are going to be saving money as a result of that decision.

This is speculation, but the answer to your question is yes.

DR. FALLAT: What is the half-life of IGIV, and by shifting to a longer time period, do you not actually inefficiently use the supply?

DR. BARR: Inefficiently use it.

DR. FALLAT: Yes.

DR. BARR: The half-life is every three to four weeks, and you are not efficiently utilizing

the supply. The patient are also really undertreated. We are allowing essentially what we would measure the trough level, the level of IgM in the patient's bloodstream just pre-infusion to get lower and lower, and essentially subject the patients to, you know, potentially life-threatening and serious infections.

Anecdotally, we have seen from a number of our patients, they were left with a mind-set during the shortage that, you know, we had a finite supply and it was in their best interest to really preserve that supply, because they needed it as a life-saving therapy.

So, the tendency, I think, among some patients was to try to use as little as possible to sort of stretch it out, and even from the patient's perspective, perhaps also the provider and the physician, that we are trying to not exhaust this finite supply of IGIV was sort of the mentality of the population, and I think it is still pervasive to some degree.

DR. CUNNINGHAM-RUNDLES: This is another tiny bit of background information about what the long-term effects might be, I think, of patients who are not getting enough gamma globulin, and this

is a current theme in clinical immunology right at the present time because there have been four separate articles in peer review journals discussing the lung function of patients who are being treated with IVIG.

I think the first, most stunning ones that said that 80 percent of patients who were getting the previously accepted dose of IVIG, in fact, had developed bronchiectasis. There was another article in the Annals of Internal Medicine in the fall in which 40 percent of all the patients in Holland were surveyed, their pulmonary functions and such, and coming to the conclusion that these patients were also being undertreated given again the standard dose. Those patients' dose actually was doubled.

Now, that being in the Annals of Internal Medicine, coupled with the articles from Finland, Holland, and also from France, about X-link to gammaglobulinemia patients having slow onset of pulmonary dysfunction, I think the current tenor in the United States of physicians who treat these patients will be to increase the dose rather than to decrease it.

From an academic point of view, this is

bound to trickle down, and I think that adds into the issue of how good our supply is in this case if everyone is going to perhaps add 25 percent more gamma globulin or, the worst case scenario, 50 percent more for every patient, that will have an impact again on the ultimate availability, I think.

That is certainly a tenor at current meetings regarding these patients.

DR. NELSON: Thank you, Charlotte.

DR. DiMICHELE: I just wanted to ask just for my own edification, what type of physicians treat immune deficiencies? In other words, certainly immunologists do, but what percent of immunodeficiency patients are treated by specialists who are well aware of supply, what they can and can't do, and how many are actually treated by maybe primary care physicians for whom information dissemination might be a problem, and thus, you know, the treatment inequity resulting from that?

DR. MORAN: I don't recall the exact statistic, I will say that as a caveat. We did a survey in 1995-96, and if I recall, it is something on the order of 50 percent or fewer were treated by clinical immunologists, and the majority of

patients were treated in different settings.

We are planning an update to that survey as part of the other surveys that were mentioned earlier to begin sometime in the next month of two, so we will get revised data, but there is a tendency in medicine in general, I think, for patients with these types of disorders or chronic disease to be treated much more in the primary care arena than specialists.

DR. DiMICHELE: Which kind of brings up the issue of access to care versus access to product.

DR. MORAN: Exactly right.

DR. DiMICHELE: And in terms of your figures being interpreted.

DR. MORAN: That's correct.

DR. ALLEN: You made a statement at one point about patients perhaps undertreating themselves, which raises in my mind--and I honestly don't know since I do public health, and not clinical medicine--is this product used as a home therapy, in other words, patients keeping a supply at home and doing their own infusion?

DR. BARR: Some patient home infuse. I home infuse. But they don't keep a supply at home.

Typically, the home health care agency would deliver the product, you know, the day of the infusion for the patient to self-infuse at home or to have a nurse infuse at home. Many patients are infused in hospital outpatient settings, also in physicians' offices.

MR. RICE: Tom, you mentioned the same thing that Dr. Weinstein had mentioned, that two of the five companies are planning to merge, and I can understand perhaps--I don't know you have responded to that or what kinds of assurances you have been looking for in light of that--I mean I can understand that maybe there is an efficiency and maybe a bolus amount of product that might occur from a concentration of resources, but as we have seen in the hemophilia community the catastrophic shutdown of Cogenate from the Bayer Corporation, when there is fewer people manufacturing a product and one goes down, it is even worse no matter how good the bolus amount might be for short term, what about that long-term picture and how that might affect you?

DR. MORAN: That is really the basis of my comment, if you go down from five sources to four, then, you are increasing your exposure, as you just

stated, as an arithmetic certainty.

With respect to potential benefits, and so forth, the companies have come to us and described what their objectives are, and we are in discussions with them about that, but I think the reason for mentioning that, and also referencing the two companies under consent decree, is again just a simple sense of vulnerability that fewer sources of product would entail.

DR. HOLLINGER: I take it that most of these are IgG deficiencies, not necessarily IgA or IgM, and what is considered a critical level of IgG in individuals? Like we have critical levels for so many other things, what is considered a critical level, understanding that there are variations?

DR. MORAN: I think we will refer that question to Dr. Cunningham-Rundles, who is right at the table.

DR. CUNNINGHAM-RUNDLES: I think most of the patients who are infused these days have the diagnosis common variable immune deficiency or substantial antibody deficiency with IgG deficiency. So, common variable is when two of the three subclasses, or two of the three isotypes are down, so IgG, usually A and very often M as well,

so it can be across the board.

People with just plain IgA deficiency generally don't get gamma globulin, though.

DR. HOLLINGER: And a critical level, what, 500, 300, 200, 100, 20?

DR. CUNNINGHAM-RUNDLES: That's impossible to say because you can have a person who has a level of 300, and have wonderful antibody function, or a level of 1,000 and terrible antibody function, so the level of gamma globulin isn't so important as the real functional component. So that has to be measured separately.

If you have to give a textbook answer, you would say that normal people run, say, 500 to 1500, that normal is normal. So under 500 is not normal exactly, but you might become symptomatic at, say, 400 or 300, certainly much less than that

DR. NELSON: What proportion of the IVIG is used for primary immunodeficiency as opposed to other, like off-label uses? My impression was that the latter has grown rather dramatically, but do you have any data on that?

DR. MORAN: Well, primary immunodeficiencies are one of I believe it is six license indications, and I think estimates vary

between 20 and 30 percent, probably on the lower end, 20 to 25 percent would be used by primary immune-deficient patients.

The other license indications may account for another 25 percent, and off-label indications may be 50 percent or higher. This is speculative. It is based on some research, but it is a guess up to a point.

DR. DiMICHELE: I have another related question. If I understand correctly, FFF was involved in creating emergency depot systems for distribution of product during shortage, and I was wondering if you could comment on the role of emergency depots in sort of alleviating the shortage, getting product to patients, et cetera, what role did it play in this shortage?

DR. MORAN: Well, in fact, FFF was the distributor that the IDF selected to handle what we call our Safety Net Program, and I think between the fall of 1998, really through the present time, there has been a substantial amount of gamma globulin distributed through the mechanism.

It was literally a lifesaver in our community, and it was done very efficiently and very effectively. The typical kind of call that

would come in would be from a nurse or a pharmacist or a physician saying I have got three patients coming in on Friday--maybe this call came in on a Wednesday--and we can't get any IGIV, and so it was really day after day, month after month, and it became year after year of filling those kind of just-in-time requests.

We frankly think that that turned the tide within our community because, as someone pointed out, if there is 5-or 6 million grams consumed by primary immuno-deficient patients, even during the shortage when there were 15 million grams released, it is a question of trying to allocate that product, target it at the patients who arguably will certainly need it with respect to life-sustaining reasons.

So, as soon as it became known pharmacists, hospitals, physicians, and patients that there was this resource available, this just-in-time resource, as a backup, I think that went a long way to ameliorating the negative health effects that Dr. Barr alluded to. At the IDF, we are very proud of that, and FFF did an outstanding job in supporting us in that.

DR. FITZGERALD: This is maybe more to

Mary than to you, but the discussions, one of the things you mentioned in your presentation was homeland defense. In discussions of responses to bioterrorism, some of the protocols that have been discussed include using IVIG versus IM.

Is there somebody looking at the possible or potential for how much might be needed and what protocols would be addressed for that?

DR. CHAMBERLAND: I, myself, can't speak directly to that, but I do know that there are people both at CDC and certainly at the FDA, that are involved in a lot of the discussions in consideration.

I don't know if anybody from FDA is present to supplement.

DR. EPSTEIN: Part of the issue has to do with vaccinia immune globulin, and the question how much can be generated, how soon, to support any kind of vaccination program, either of first responders or in circumstances of an outbreak, and research mainly by scientists at FDA has shown that there are IGIV preparations that contain levels of antibodies to vaccinia due to childhood immunizations, which stopped in the very early seventies, and that the titers are lower than in a

fresh vaccinee, but are potentially useful.

So, there is the question whether one could utilize any existing stocks of IGIV to deal with any large number of vaccinee or vaccinations, smallpox vaccine, so we are aware of that, and we are looking at it, and we are also aware of the possibility that one might be able to conserve product use by IM dosing versus IV dosing.

But I just think that all of those issues are very much under discussion and that there is not much that I could say definitively except that it would potentially become yet another medical demand for IGIV products.

DR. NELSON: Thank you.

The next item is a discussion of the recent HIV Western Blot shortage.

Dr. Mied.

Recent Western Blot Shortage

DR. MIED: Thank you, Dr. Nelson.

[Slide.]

On April 17, 2002, Calypte Biomedical Corporation of Alameda, California, issued a News Release in which it "announced that it has begun to wind down its operations." These operations include the manufacture of the Cambridge Biotech HIV-1

Western Blot Kit.

The Cambridge kit is one of three currently available HIV-1 supplemental tests licensed by FDA for testing of blood and plasma donor specimens or as an aid in medical diagnosis.

The other two licensed supplemental tests are the Genetic Systems HIV-1 Western Blot manufactured by Bio-Rad Laboratories, Inc., of Hercules, California, and the Fluorognost HIV-1 IFA kit manufactured by Sanochemia of Vienna, Austria. Performance of a licensed supplemental test following a reactive donor screen is required under current regulations (See 21 CFR 610.40(e)).

On May 13, 2002, Calypte Biomedical Corporation issued a Press Release announcing the continuation of ongoing business and that "the company does not intend to wind down its business as previously announced."

In the interim, however, pending replenishment of inventories, shortages of Western Blot Kits may continue to occur, especially for use in diagnostic testing, since that constitutes the market segment with the greatest demand for Western Blot Kits.

On May 10, 2002, in response to inquiries

from public health testing sites and clinical testing laboratories, CDC issued a Morbidity and Mortality Report, an MMWR, that outlined options for clinical testing laboratories and public health laboratories for supplemental testing to detect HIV antibodies using test kits approved by FDA in the event that the Cambridge Biotech HIV-1 Western Blot Kit is unavailable. Some blood and plasma establishments have also experienced delays in obtaining HIV-1 Western blot kits.

[Slide.]

The following current options exist for blood and plasma establishments for use of licensed HIV-1 supplemental tests to validate the results of donor screening for antibodies to HIV:

First, use a licensed Western Blot Kit. Supplemental testing can be performed on serum and plasma using the Genetic Systems HIV-1 Western Blot (Bio-Rad Laboratories, Inc., Hercules, California). Information about the availability of this test kit can be obtained on-line at www.biorad.com or by contacting the company directly at 1-800-2-BIORAD.

The Cambridge Biotech HIV-1 Western Blot Kit may also be available for use. Information about the availability of this test kit can be

obtained on-line at www.calypte.com or by contacting the company directly at 1-877-CALYPTE.

The second option is to use the licensed Sanochemia IFA test.

Supplemental testing can be performed on serum or plasma using the Fluorognost HIV-1 IFA kit manufactured by Sanochemia, Vienna, Austria. Information about the availability of this product can be obtained by accessing the product web site at www.fluorognost.com or by calling Fluorognost at (203)-227-6880. Sanochemia provides both a self-taught course on performing the HIV-1 IFA and a proficiency panel free of charge.

[Slide.]

Future Options for Consideration. In the event that approved supplemental tests become unavailable, FDA would consider whether it is appropriate for establishments to use under the IND mechanism foreign supplemental tests that are brought forward in pursuit of licensure.

FDA is also interested in facilitating the development and approval of alternative testing strategies that could provide additional options for supplemental testing of blood samples from donors with reactive screening tests for HIV.

It is our current thinking that additional options for supplemental testing might be developed based on suitable scientific data contained in application submissions, for example, the validation of nucleic acid testing, or NAT, for use in supplemental testing algorithms.

Scientific considerations suggest that a reactive NAT on an individual unit could be taken to confirm a repeatedly reactive screening test for antibodies to HIV. Conversely, a negative NAT might be taken as conclusive in some circumstances. FDA would review data from studies performed by industry should they wish to pursue such options.

Secondly, a role for reference laboratories. FDA is interested in hearing comments on the issues related to the creation of a role for reference laboratories in providing supplemental testing for antibodies to HIV.

Thank you.

DR. NELSON: Thank you, Dr. Mied.

Questions? Yes, Paul.

DR. SCHMIDT: Of the, is it 13 million units of blood collected in the country a year, what number are going to require this supplemental testing, and how does that face up to other uses of

the supplemental test in diagnostic clinics, and things like that? How much of the problem is a blood supply problem?

DR. MIED: In the donor setting, the repeatedly reactive rate for HIV antibody is approximately 0.1 percent or 1 in 1,000. So, out of 13 million donations of blood only, we are talking about 13,000 HIV Western blots would need to be run.

We have found that the total market for HIV Western blot testing is approximately 35,000 tests per month, so if you look at it on a percentage basis, the blood and plasma market plus military testing, on the whole, totals no more than 10 percent. From what we can see, the diagnostic testing market is about 90 percent of total Western blot demand.

DR. SIMON: In terms of your possible future options, I wasn't clear what you meant by a role for reference laboratories. How would that help if there is a shortage of test material?

DR. MIED: There may be existing laboratories that could qualify as reference laboratories for the purpose of providing supplemental testing, or perhaps a whole new

laboratory structure could be created.

We would welcome comments on possible options as to how this could be done, how it could be provided perhaps as a service.

DR. SIMON: But wouldn't the reference laboratories use commercial reagents, or are you saying that they would use some other source?

DR. MIED: They would use commercial reagents, but we are certainly interested in listening to alternatives, and those alternatives, as I said, could include new alternative testing algorithms that could be approved, that could obviate the need for Western blot.

DR. NELSON: Actually, since blood donors are screened with NAT, those that are NAT-positive wouldn't need a supplemental test. Would that solve a lot of the problem as far as the blood donors are concerned?

DR. MIED: Dr. Nelson, currently, they are screened with pooled sample NAT, and you may have a repeatedly reactive test from an EIA, a sample that is repeatedly reactive with on EIA, but is negative on pooled sample NAT, which on subsequent testing could be reactive on an individual sample NATION. This is the type of data FDA welcomes, how such an

algorithm could work.

DR. NELSON: I guess if the person was on therapy, that might happen, I agree.

DR. ALLEN: Are there currently manufacturers, particularly the NAT testing, who are considering submitting the data that you are asking for, or is this really perhaps way down the line before that might become a possibility?

DR. MIED: No, we don't think it's way down the line. We know there are some studies in progress right now. We will have to see what the result in, in terms of product submissions from the manufacturer.

DR. HOLLINGER: Paul, at 35,000 tests a month, that does not seem to be a large number. Why is it that the manufacturers are not producing the Western blot kits? What is the reason that there is a reduction in these kits?

DR. MIED: Well, at time we had four licensed Western blot manufacturers. One has ceased producing Western blots, but another one was the Genetics Systems' Western Blot, which has continued on the market even though Bio-Rad, which had another of the licensed Western blots, now Genetics Systems is part of Bio-Rad, so we have

lost one Western blot being a manufacturer has discontinued production of it, and the other one was a company with essentially two products that decided to go with one.

So, we current have two licensed Western blots, and we are interested in doing what we can to encourage more manufacturers to get into supplemental test production.

DR. NELSON: Jay.

DR. EPSTEIN: Thanks, Kenrad.

I just wanted to follow up because I think that what you are hearing, similar to the presentation on IGIV, the FDA does not control the market forces. We do what we can to work with manufacturers either to get them into compliance or to help them streamline their product submissions, come to license more quickly, and so forth.

But I think what you are hearing is that there are these forces that make the market irrational, but we don't control them, and what we are looking for are ways to perhaps better engineer the public health system, so that we are able to have safeguards, either providing products for patients with critical need or making critical diagnostics available, still under the general

umbrella of licensed mechanisms and quality oversight, but to do something about the fact that we have these irrational market forces.

DR. HOLLINGER: I understood that, Jay, but I guess my question was a more generic question of why, I mean if the market is out there, is it liability, are there other issues that they just don't have the manufacturing to produce these kits or something, is it not profitable? I am just trying to figure out what is the reason why there is this issue here.

DR. EPSTEIN: I don't know that I am in a better position to answer that question than anybody else. I can tell you what we heard. The things that we hear are that these are not profitable products.

We hear that producing them under GMP creates a barrier. We also hear that companies basically want to make home run products, there is not a lot of incentive for the companies with the capability to make these products, to make products that have small volume sales.

These are just the kind of things that we hear.

You know, every company wants to sell

millions of screens, and few companies are willing to make products that are only a few tens of thousands of supplemental tests.

DR. HOLLINGER: Does this mean that perhaps in the future, for products like this, that are going to be required, and so on, that they are going to have to be manufactured by the government then or something else if they are not going to be picked up by industry?

DR. EPSTEIN: I think that that would be one sort of option that could be considered. This is why we are saying we need to call for options. There are other ways one could look at this.

For example, the blood industry itself could establish a reference laboratory using licensed reagents. If they are not available from other sources, that entity could itself become a manufacturer, but it could be linked to a stable revenue, because it is sponsored by the organizations that need to use the product. The blood product testing would be done by laboratories supported by and then serving the collection industry.

So, there are ways that the thing could be stabilized. The government I think has reasonable

reluctance to just step in and become a manufacturer, it doesn't want to do that.

DR. NELSON: Yes. The microphone.

MR. STEVENS: Chip Stevens from Sanochemia Fluorognost, makers of the Fluorognost HIV-1 IFA. I am not here to talk about our product, this is not the place. It is an FDA-approved product with very high quality sensitivity and specificity.

On the request of the CDC and certain members of the FDA, when the Cambridge issue came up, we increased our production 3-fold to meet the crisis. Since the crisis started, half of the state health departments have been qualified on our test, and have either established it as their test or as a Plan B.

In that time, but one blood center has called us. We, at great financial risk, we are a company that produces one diagnostic product. The HIV-1 Western Blot costs about 13 to $14 to manufacture and produce, get out on the market. Most people are willing to pay about 13 or $14 for that, and that is a reason you have a shortage, that is why you have companies merging, going out of business.

We produce an IFA product, a very quality

at great financial risk, we built our inventories and have not gotten much of any response from the blood bank. I would request before you look at lowering the standards, holding a safety net for NAT, using that as your confirmatory, that you look at the market itself.

We work real hard. We don't want to be another manufacturer that goes down trying to help the market, meet the marketplace. We have product available, and we are ready to meet the marketplace need.

DR. NELSON: Thank you. Mike.

DR. BUSCH: Mike Busch. I personally think, well, one, is that we pay about $50 per strip for Western blots. That is the discount rate, large volume purchases, but in a sense, you know, the problem is the rest of the world is long past Western blot and IFA's. They are using recombinant antigen-based supplement assays that perform very well in a sensitivity/specificity context.

The problem is the market is so small, and the barrier, the cost barrier, to produce and license these products through FDA, has led to the failure of most of these products to come formally

to FDA.

The few examples where I have been involved where recombinant-based assays have come to FDA, the criticism historically was that, you know, you look at lots of seroconversion panels and you will find that they can't always pick up when the most sensitive EIAs can. They are better than blots, but they are not as sensitive as the EIAs in certain panels.

Now, that is a dead issue since we screen the blood supply with NAT, so we have RNA to cover that early window period, but still the fundamental problem is I just don't think any of these companies are going to bring state-of-the-art assays to this country for full FDA licensure, and I think the option of trying to figure out some way where large blood center or other reference labs can gain access to these products and perform them in a context that FDA accepts is the best solution.

DR. STRAMER: Susan Stramer, American Red Cross.

I just want to make the committee aware of two points. One, the accumulated NAT data we have, and NAT has been referenced as one possible alternative to the Western blot, where that is an

option for NAT positives whether they are detected in pools and then resolved to an individual donation, that is all well and good, but that represents only 5 to 7 percent of the total usage of Western blot. So, that will eliminate only a small portion of the need.

Then, if you look at the Western blot positive, the other side of the coin, are the Western blot positive samples that aren't NAT negative, as Dr. Nelson mentioned, if an individual is on treatment long term, non-progressors who may have very low viral load.

In our screening program at the American Red Cross, we found 41 such samples that are Western blot positive and NAT negative, so to look at options to decrease the burden on the supplemental tests, which even when they are FDA licensed lack the same quality as our primary screening tests, what we are doing, that is, Red Cross, in collaboration with Blood Systems Laboratories, is we are validating a dual EIA strategy, the same as we use for HTLV today because of the issue of no supplemental test that is licensed by FDA.

So, what that would entail are the two

tests that are FDA licensed for screening that have been through the most robust validation, the largest amount of data accumulated from users on the test, and probably the most confidence that we have on any test kits available.

So, we would do the dual EIA the same way as we apply the HTLV algorithm, and only concordant EIA repeat reactives would go on to Western blot for further resolution, and discordance would not require any testing.

So, if testing about 500 Western blot positives that are NAT positive, we found that to be reactive on both EIAs--this is data to date, we are not completed with the study yet--and of Western blot indeterminates and negatives, we are able to eliminate over 90 percent of repeat reactive samples on either of the two screening tests, so this will greatly diminish the burden of volume that is required for the supplemental tests.

So, we believe that this will be a viable option. Our plan is to collate the data provided to FDA for review, and hopefully, have further action at that time.

Thank you.

DR. NELSON: Thank you. There is also a

lot of data in the international setting using that algorithm of dual EIA, and the data so far is pretty good. Of course, they are often in higher prevalence populations than the donor population, so I think it needs to be looked at in the blood donor population, as well.

Toby.

DR. SIMON: I think we have had two very interesting presentations on significant shortage issues. I think Dr. Epstein's comments are very good in terms of focusing us on the fact that the market forces can be irrational, can cause problems.

I do think, as this committee discusses this and other items, one of the things we need to keep in mind is that the cost of regulation has a heavy impact on these markets. We are looking at, I think, a number of instances in which the cost of regulation may have impacted supply, and that is something I think that needs to be considered as we look at the economics and its impact on patient care.

DR. NELSON: Somebody mentioned the--maybe that was the IVIG--the consent decree, a few companies, was the consent decree related to this

product production or something else, do you know? Were they related to GMP problems with manufacturing this product or some other product?

DR. MIED: Not for the Western blots that I am aware, no.

DR. NELSON: Wendy Chen from Calypte.

DR. CHEN: Thank you, Dr. Nelson. My name is Wendy Chen. I am the director of Product Technology at Calypte Biomedical Corporation. I would like to thank the committee for giving this opportunity to read the following statement.

Calypte Biomedical Corporation, headquartered in Alameda, California, is a public healthcare company dedicated to the development and commercialization of urine-based diagnostic products and services for HIV-1, sexually transmitted diseases, and other infectious diseases.

Calypte's existing products include the Cambridge Biotech HIV-1 serum Western Blot supplemental test, as well as the only two FDA-approved HIV-1 antibody tests that can be used on urine samples - a screening EIA and a supplemental Western Blot.

On April 17, 2002, Calypte announced that

the company had begun to wind down manufacturing operations and might file for bankruptcy. Faced with limited operating cash, Calypte began laying off its workforce and closing its facilities while at the same time, continuing to aggressively seek partnerships and additional funding.

Calypte announced that we would not longer be able to sustain operations from existing revenues and current financing lines.

On May 13th, Calypte received a commitment for investment in new equity from a group of private investors to be used to fund the Company's operations and to move forward with the implementation of its business plan.

In light of this new funding, operations in our Alameda, California and Rockville, Maryland production facilities were not completely shut down, key staff were brought back and production was resumed.

On May 24th, Calypte announced the completion of $2.7 million in financing.

To date, Calypte has been able to bring back 42 key employees and because steps were taken to allow operations to restart smoothly, we have been able to resume production of all products with

minimal interruption. Additionally, we have retained an inventory of its HIV-1 Urine EIA screening test and will be submitting additional product to the FDA for lot release in early July.

We are now happy to report that we have received FDA lot releases for new inventory of both the Cambridge Biotech HIV-1 serum Western Blot supplemental test, as well as the Cambridge Biotech HIV-1 Urine Western Blot supplemental test. All of our HIV testing products are again available and are being distributed.

Calypte looks forward to continuing to work closely with the FDA to continue to supply our HIV testing products to the market as quickly as possible.

Thank you.

DR. NELSON: Thank you. Questions or comments?

The next speaker is Chip Stevens from Fluorognost. You made a comment at the microphone. I don't know if you want to say anything else. No? Okay.

Celso Bianco from America's Blood Centers.

DR. BIANCO: We had prepared a statement that is quite long, so I will try to summarize it,

but I respectfully request that the whole statement become part of the record.

American's Blood Centers, as you all know, is a national network of locally-controlled, not-for-profit community blood centers that collect about half of the U.S. blood supply.

While we are hopeful that the anticipated shortage of HIV-1 Western blot kits has been staved off for now, the incident highlights the need for multiple suppliers of the tests for which we rely for donor counseling and donor re-entry.

More importantly, it also suggests the need for alternative approaches to the use if supplemental tests and the management of those tests.

I think this is an opportunity--and I will try to summarize this--to address the major issues that we have with supplemental tests.

First of all, the current screening tests, since they are being applied to an essentially negative population with very few positives, produce a lot of false positive test results, and we know that.

Donors with repeatedly reactive screening test results, they must undergo confirmation

according to the current regulatory process. The number of HIV tests for confirmation is limited. There are no confirmatory tests or additional more specific supplemental tests for the other retrovirus that we test for, this HTLV I/II.

The current supplemental tests, like HIV Western blots are less than optimal, and I must mention that the Cambridge Western Blot has in its package insert that when it is supplied to a normal population that is negative on the ELISA screen, that Western blot will produce 15 percent of the time indeterminate test results simply because of the definition of negative as stated in the approval of the test.

I mentioned the HTLV, and even in the case of HTLV, there was a question from Dr. Paul Mied about laboratories. There are laboratories, including one laboratory that is the State of California laboratory, that will provide confirmation, for instance, for HTLV using home brew tests that they have developed, but those are not tests licensed by FDA.

If we look strictly at the Final Rules on Donor Notification that were issued on June 11th, it says that we must attempt to obtain results of

supplemental tests obtained under 610.40, and all the rules require that we make the confirmatory tests as part of the donor screening process even if subsequently we do not re-enter the donor.

We believe that there are potential solutions. Dr. Stramer just mentioned one approach that I think very interesting and useful of the dual EIA that she is doing in collaboration with Sally Caglioti from Blood Systems.

There are other potential ways by which we could approach it. I am not choosing one, I am just raising them. I would like to see all of us think outside the box and get out of this trap of the screening and the supplemental tests.

One thing that is very important, FDA has contributed a lot in the presentations before, about a year ago, to this committee on the approach to donor management after NAT licensure. We would like to see that guidance out. We like the schemes, we like the fact that it resolves, for instance, indeterminate Western blots in a way that we could not resolve before.

We would like, at the same time, to revisit the Western blot criteria and get rid of the issue of non-viral bands as indeterminate,

because today we have a much better armamentarium, much better tools to resolve those issues.

We would like, even if it is a small number, as Dr. Stramer mentioned, not to have to do a Western blot or a RIBA after we have a screening test that is positive for HCV and a NAT that is positive.

This donor is positive. The performance of RIBA in this situation just delays the notification of the donor, delays the initiation of lookback, delays the implementation of treatment, let's say, for HIV, even with the risk, and counseling, even with the risk of secondary transmissions.

We would like to think maybe that when we have no chance of resolving the Western blot or the confirmatory tests or the supplemental tests for HTLV, and it is unlikely that we are going to see one, maybe to classify these individuals as patients, and allow the current medical system that can use research tests, that can use other approaches, to attempt to resolve the future of the those donors. The only thing that we have to do for the safety of the blood supply is not to re-enter these donors.

We can consider revising an evolving system as new tests, new technologies come up, to consider changing those confirmatory algorithms instead of just being part of strict regulatory mechanisms.

Finally, as a suggestion, another suggestion, we would like FDA to, as in the case of what happens now with the licensure of the NAT for HIV, and allowing the elimination of the HIV p24 antigen screening test, that the donors that have been in the past deferred because they had nonspecific test results of p24, to allow essentially an automatic re-entry of those donors, because at that time, it was the lack of power of the resolution systems that did not allow these individuals to be entered. Today, with NAT, they could be eligible to donate.

ABC hopes that FDA will use this opportunity to revise its regulations, promote new technologies for blood donor screening and for supplemental tests, and apply current scientific information on the epidemiology of transfusion-transmitted diseases to rationalize donor deferrals, notification, counseling, and re-entry, and we are ready to help in any way we can.

We accept the challenge from Dr. Mied that we have to produce the data.

Thank you.

DR. NELSON: Thanks, Celso.

Questions or comments?

Thank you.

The next person that will present is Christopher Bentsen from Bio-Rad.

DR. BENTSEN: Good morning. I would like to read a brief statement into the record.

Bio-Rad Laboratories, Genetic Systems Brand, HIV-1 Western Blot was licensed by the FDA with the use of serum plasma and dried blood spots on November 13th, 1998. This was the fourth and most recent Western blot license by the FDA and appears to be only one of two remaining Western blots on the market.

Bio-Rad Laboratories acquired the Genetic Systems Western Blot when it purchased Genetic Systems Corporation and Sanofi Diagnostics Pasteur on October 1st, 1999. Over the past year, Bio-Rad Laboratories in Redmond, Washington, has increased production of the Western Blot Kit in order to meet the increased market demand, and based on Company estimates, Bio-Rad believes it can meet current

customer demands for its Western Blot Kits by the end of this summer.

Thank you.

DR. NELSON: Any questions?

All right. Thank you very much.

Finally, Bruce Phelps from Chiron Corporation.

DR. PHELPS: Thank you, Dr. Nelson, for this opportunity to speak with you this morning.

[Slide.]

I would like to bring to the attention of the committee an alternative to the Western Blot which Chiron Corporation has manufactured since 1996, and that is the RIBA HIV-1/HIV-2 strip immunoassay. This particular test was submitted to the FDA for review in 1996.

[Slide.]

There were several concerns raised by the FDA after this review of the submission in 1997, in a list of questions that came back to Chiron Corporation. Among those concerns listed on this slide there were some performance issues relative to equivalence to the Western blot, interpretation of the plus/minus band densities on the antigen bands that were developed during the assay, and

also the lack of HIV Type O specific sequences in this particular assay formulation.

I would like to provide some information and data on the performance of the assay relative to these aspects in later slides.

Similarly, there were a couple of manufacturing issues that were of a concern, lot-to-lot reproducibility in particular, variability of the IgG control band densities, and process and methods validation issues, and I would like to just touch base momentarily on those issues also.

[Slide.]

This is a summary of data from a publication that was published in the Journal of Clinical Microbiology by Kline, et al., in 1996. It was a population of HIV-1 and HIV-2 positive specimens, as well as a fairly significant number of negative specimens that were tested, and this shows the performance of the kit relative to the Western Blot.

As you can see, in terms of sensitivity, its sensitivity was significantly increased specifically with respect to HIV-2. In a population of 215 specimens, the RIBA test correctly categorized all 215 as HIV-2 positive,

whereas, the Western Blot--and this was the Cambridge Western Blot, by the way, that was tested in this study-- only 158 of those specimens were actually correctly called as positive, and 57 fell into the indeterminate category. So, there is an improvement in sensitivity with the RIBA.

In this particular population, we did miscall one as a confirmed positive on the HIV-1. It fell into an indeterminate category. With RIBA, an indeterminate is any kind of a band pattern that does not meet the criteria for an HIV-1 or HIV-2 positive. It's a 1 plus, but there may be other plus/minus bands that are present, that are just above the level of detection, but aren't dark enough to be considered a positive 1-plus band, so they would fall into the indeterminate category.

With respect to the specificity, as you can see, there were three that were falsely positive on the RIBA test, two, HIV-1 and one, HIV-2, however with the Western Blot, five of these individuals were designated as falsely positive, so there is an improvement also in specificity with respect to false positivity.

There were 22 of these individuals that fell into the indeterminate category on RIBA, but

152 in terms of the Western Blot, and only 391 were actually correctly called negative by the Western Blot, whereas, 523 were called correctly by the RIBA. So, there is a significant improvement in terms of specificity with the RIBA assay also.

[Slide.]

With respect to the plus/minus band density, this was a concern of the FDA relative to the interpretation of the plus/minus bands. Ordinarily, they are basically interpreted as negative, which leads to these sensitivity and specificity data. This is using the data from the last slide just as an example.

Under those conditions, you remember there was one of the HIV-1's that were missed, so that gives a sensitivity of 99.8 percent on HIV-1, but 100 percent on the dual infectives and on the HIV-2's. With the three false positives, that is a specificity basically of 0.6 percent with RIBA.

If we were to call the plus/minus bands positive, I think as was suggested by FDA, we would obviously throw this HIV-1 into a positive category, giving 100 percent sensitivity across the entire population, however, this estimates that all of the indeterminates would probably fall into the

positive range also, and this is probably a best case, because there would be some of the negative populations in this particular instance that would have had multiple plus/minus bands, and a plus/minus is considered positive. Some of those would be thrown into the positive category also.

So, you can see the specificity of the test is significantly impacted and becomes much reduced, and any of the advantages over Western Blot would be lost.

So, that is an issue that would need to be resolved with this assay, we understand that.

[Slide.]

On this slide is shown the HIV-1 subtype sensitivity. We did look at multiple HIV-1 subtypes all the way A through F, and particular O. There were 45 specimens, Type O specimens that were tested, and you will see in this particular instance, all of these, all subtypes were detected as 100 percent as HIV-1 positive, so even though there is no specific antigen sequence for HIV-O, we do detect it in the RIBA and would correctly confirm those samples.

[Slide.]

In terms of manufacturability, since 1996,

when we started manufacturing this material for ex-U.S. markets, we have produced 15 lots. That amounts to over 10,000 kits and over 315,000 strips.

In 2001, last year, we sold 942 of these test kits in multiple markets around the world. You can see the 10 countries listed here where we have entered in the market and are continuing to supply adequately to support supplemental testing in these markets.

Also, just this year, we are entering the market in Brazil and Venezuela and in Mexico. So, you can see that in ex-U.S. markets, this is a viable alternative to Western Blot and has been accepted by many users as a reasonable means of confirming HIV positive results.

[Slide.]

Also, in that time period, we have produced multiple lots of the antigens used on the strips. In this instance, you can see five to six lots since 1996 of each of the antigens that have been used and that are coded on the strip, which leads us to some of the validation issues.

[Slide.]

With that number of lots that have been

produced since 1996, we would anticipate that it should be acceptable and enough to allow us to utilize retrospective validations as a means of confirming the manufacturability of this particular kit and these reagents.

This is somewhat related to the issue that was brought up recently about the cost effectiveness and the profitability of these kinds of assays. If we were to do prospective validation as required by the current regulations, that would require at least 24 antigen lots at an estimated cost of almost $5 million for us to produce.

In addition, we would have to produce three, full-scale RIBA validation lots at almost another million dollars plus the verification testing, to a total of about almost $6 million just to do complete prospective validation under the current regs.

Our estimate is for the total HIV supplemental testing market in the U.S., for the Western Blot, is currently only $0.8 million. So, you can see there is really no cost effective way that we could continue to satisfy the regulatory requirements and, at the same time, provide what the market needs for supplemental testing.

But I did want to bring this to the attention of the committee. This is an alternative that we have produced. We are producing it for ex-U.S. markets very effectively, and if the FDA saw fit to provide some additional focus on this, we would be willing to consider bringing this forward as an alternative to Western Blot.

Thank you.

DR. NELSON: Thank you, Dr. Phelps.

Questions?

When you did the validation testing, you tested a number of samples that were negative on the EIA, but that isn't the way the test would be used, right, it would be a confirmatory test where only EIA positives would be tested?

DR. PHELPS: That is correct, yes.

DR. NELSON: So that the nonspecificity shown in your data shouldn't be a problem if the test is used the way it would be planned to be used. The real issue is the sensitivity of the true positives picked up in this.

DR. PHELPS: That is correct. In the clinical validation, however, it is required to show specificity with negative populations, and that is why that data was generated, but you are

correct, it would only be EIA repeat reactives that this test ordinarily would be used with.

DR. NELSON: I am surprised that the Western Blot didn't have a higher problem with nonspecificity than shown in your panel, because when there have been vaccine trials where people prior to receiving vaccine, HIV vaccine, have been required to have Western Blot even if the EIA is negative up to 10 to 15 percent of the population has been excluded based on bands on the Western Blot.

DR. PHELPS: Right. Again, that particular study was with confirmed HIV-1, HIV-2 specimens, so it has already gone through a number of screens prior to that, so that is why the data looked fairly clean.

DR. NELSON: Thank you.

DR. BUSCH: Your comment about vaccine trials is I think very important because we are beginning, in blood donor settings, we have picked up a small number, but a number of donors who are false positive on the IM Western Blot, but who were so because of vaccine trial participation. You know, these vaccine trials are beginning to expand here in the U.S. and globally, and there is a clear

need to develop screening and more important supplemental assays that can accurately discriminate vaccine responses for infection on top of a vaccination.

I think one of the problems that we have is that the companies that have the capacity to develop appropriate recombinant antigen-based supplementals are simply not participating in the market in bringing these assays forward particularly in the U.S., so just another issue that makes us, to me, need to get companies like Chiron and Intogenetics, et cetera, somehow bringing assays into the U.S. market.

DR. FITZPATRICK: Since the blood donor screening market is only about 10 percent of the Western blot market, have you looked at what the clinical market for RIBA is as a diagnostic?

DR. PHELPS: In terms of the total--again, I am not trying to make a business case of that last slide--but in terms of the total Western blot that we sell through Ortho Clinical Diagnostic, in our joint business with Ortho, that 8/10ths of a million dollars represents the entire market for both diagnostics and blood screening.

So, if you take the total testing that is

done, Cambridge and other Western blots, is probably around 1 or 1.2 million I would expect maximum in terms of a dollar market.

DR. CHAMBERLAND: I just want to clarify also on that slide, you had these various costs that totaled 5.8 as prospective validation, that is ongoing validation, not a one-time thing, but something that would be done on an ongoing basis? Could you clarify?

DR. PHELPS: Right. That would be the cost whether we decided prior to approval to provide all 24 lots and 3 lots of RIBA or if we did it as a concurrent validation. That would be one alternative, is to move forward producing the material, but making these lots concurrently and then providing the final data package to FDA for approval, but that would be the total cost of what we estimate to be required by the current regulations.

That means 3 lots of each of the antigens and 3 lots of the final kit at full production capacity.

DR. LEW: Since you did bring up the business aspect, though, just calculating the numbers from what other people have said, if there

is 35--that is what I heard, I think, 35,000 kits, or how many kits--

DR. PHELPS: 35,000 tests is what I understand.

DR. LEW: --tests that are needed per month, that is, by year, 420,000, I mean to me it seems like we are guessing that there is only $2 million profit total for all companies? That doesn't quite make sense because those kits are kind of expensive.

DR. PHELPS: I would have to defer to others with respect to the total diagnostic market. I know for blood screening--

DR. LEW: Blood screening is only 10 percent, I know you mentioned that.

DR. PHELPS: Correct.

DR. LEW: But when they were talking about all clinical diagnostic use, it was 35,000, so that is almost half a million, I mean close to. It seems like there is more profit out there than is being stated.

DR. PHELPS: I understand that that number was raised. I can't confirm that it is 35,000 a month. I only know the blood screening particularly.

MR. STEVENS: Just from our figures, marketing, and to back up the FDA's figures we were given, it is approximately 35,000 tests a month. The IFA and Western blot, average selling is above $20, which brings you about $8 million a year.

DR. NELSON: You have also shown that there is an international market, although probably less robust, but maybe the European market is pretty good. It looks like this is not a huge profit item, but it still is critically important to medicine and public health.

DR. PHELPS: Just one added point, we are also in the process of producing a RIBA HTLV kit also, as you are aware of, Dr. Nelson.

DR. FITZGERALD: If we combined the ABC statement and looked at two different aspects, because we are actually looking at two different things here, one is deferring a donor and releasing or not releasing a unit, and the other is following up the donor and determining whether the donor should be a patient, so if we look at the ABC statement, which suggested that the supplemental tests not be donor screening tests and fall under that validation criteria, but be a diagnostic and fall under that criteria, do you know or would

anybody have an estimate of the difference of bringing a test to market in that respect versus as a donor screening test?

DR. PHELPS: My understanding, at least as a manufacturer, is that even in the context of a diagnostic test, the validation criteria still remain the same. The only difference, at least with HIV, that I am aware of is that the FDA, I believe has indicated that for diagnostic tests, the Type O specific sensitivity is not a requirement as it is for screening tests.

DR. NELSON: Any other comments?

Thank you.

DR. PHELPS: Thank you.

DR. NELSON: The next item is an informational item on Electronic Submission of Applications. Michael Fauntleroy.

Electronic Submission of Applications

MR. FAUNTLEROY: How are you? I am not the scientist, I am not the IT guy either. I am the policy and guidance person within CBER, who is responsible for bringing us in to the 21st century.

If we could take a moment right now and just think for a second. When most of us were in high school, we didn't have computers, we didn't

have condensed mikes in front of us as we do, everybody on the panel.

Most of us are carrying cell phones, pages, or PDAs, and so it is logical for us to move forward as a review, agency review center for this regulated industry to move into the 21st century, and my task today is to bring you some information about how CBER is moving forward into the 21st century.

But before I move forward, I would just like to thank you for the opportunity to do this, because I enjoy this challenge.

Now, if I can remember technology, okay, here we go. I am not used to this aspect of the technology, and generally have the computer right here or I have a gentleman in the room presently handle my slides for me.

[Slide.]

What I would like to talk to you about today, as you see before you, is a series of items. Don't worry, I am not going to go through all 132 slides, I don't have the time. I would love to because it's important good information, but I am going to talk to you today about our philosophy and maturation within CBER, our electronic document

room, and hopefully, within the 30 minutes I have been allotted, the electronic IND and secure e-mail.

Secure e-mail is the newest, hottest thing within the Center, and I am sure that you will be very interested as we have been hearing all these business case discussions, well, this was a program brought forward as a response to business' desire for more rapid communication with us.

[Slide.]

Our basic philosophy is one of partnership. In this world of regulated industry, we are looking for feedback from you and with you in the development of the electronic document paradigm.

Now, we encourage within this communication. Why do we encourage communication? Because it is very hard from a guidance document or from any other manner of communication except person to person, to understand individual thoughts.

Now, if you think about it here for a second, the majority of the crowd in here has either been married, is married, or divorced, and one of the biggest problems in there is always

communications. You can never get it from a piece of paper, you have to sit down and wrestle with it person to person. This is why I have my e-mail address and my phone number on the covering of every slide. We need to talk.

But what do we talk about, because in this day and age of electronic documents, you could have a plethora of things going on? Well, we talk about standards. The guidance brings forward manners in which standards for information dissemination should be utilized, and at the end of the day, we hope to be in the same place where the reviewers who have been trained on utilization of different documents will be able to use and leverage their experience from document to document because they are being brought forward in a consistent manner.

Now, these documents are fully modular. What is the advantage of fully modular presentations? Well, for industry who are putting together these various submissions, this means that your regulatory affairs group, your clinical writers, and various other groups that are involved in this process don't have to wait until the last minute to try and get a document put together.

You can start when you finish your

development of the product, put your CMC section together. You can then, as you have your clinical reports put together, paginate those individuals in the electronic submission paradigm, put those together. It is a plug and play. As you finish information, you can put it into context. You do not have to wait for everything to be done to go to the next step.

Now, how do our reviewers access this? Well, information access is done through a series of items, either through the roadmap to get to the table of contents paradigm that we have, through submission indexes which allow word searches on various items that are put into the document, so if you want to find a Western blot, information on that within the submission, you would type that into your Adobe interface and it would give you the series of hits of the use of Western blot within the document rendition.

Folder structures. Well, if you don't like individual tables of contents, you can go to the submission within our electronic document room--which I will be talking to you about--which will allow a reviewer to go to the item that they are responsible for, get to that item's table of

contents, and move forward.

In essence, we are allowing for faster information access through the use of the electronic submissions paradigm, which brings us to this point, that we are also in guidance development for PMAs, 510(k)'s, IDE's. We have presently already accomplished the paradigm for the IND and the BLA, and all the multiple iterations of the BLA, such as the rolling BLA, the ECTD BLA iteration, because of the advent of the CTD's adoption, and other items. Still, the straight BLA can be submitted. These are things that are all being done within CBER.

[Slide.]

Now, the maturation process. By virtue of being able to rattle off all the items that I just have--I missed a slide and since I am not in control of my computer, I am just going to jump over it--when in doubt, ask.

That is the take-home message here. It may sound like a simple one, but when in doubt, ask. Don't wait until the last minute, don't be afraid to talk to the FDA as a regulated industry, because this is truly a paradigm that is going to flourish through information dissemination and

communication. That is what is the bottom line here. You must talk with us, there must be an information exchange either through guidance which gives you part of the picture, but not all the fine points because of the nature of the evolutionary process of electronic documents.

And please don't wait until a month before the submission to call us. Talk to us early, talk to us often. I do return all phone calls and e-mails.

Now, to the present slide, submission maturation.

[Slide.]

By virtue of me just being able to stand here and talk to you about these documents, is a sign of growth. We are receiving submissions within CBER, it is commonplace now. It does not require a great degree of panic from fear, uncertainty, and doubt by reviewers because they have never seen these documents. An electronic IND is fairly commonplace, and the submission of a BLA electronically, totally electronically, no paper copies, is also commonplace with CBER.

So, these are items and functions that you can use to expedite the review process because you

facilitate information exchange and discussions through the delivery mechanism of an electronic document.

Now, we are no longer having to discuss pagination, submission software standards. Everybody understands we have them and understand them. People seem to know what a roadmap file is and understand why hyperlinks need to be blue.

For those who don't know, we have blue hypertext links within CBER, so that whenever you see blue, a reviewer knows that there is an opportunity to access additional information. They have been seeing it this way for the four years that I have been in this position, so they understand now like any child you have trained, like Pavlov's dog, you see blue text, there is a link there. There is no ifs, ands, or buts, it's without question.

[Slide.]

Now, for an especially rewarding and challenging discussion from a development impact is the Electronic Document Room.

[Slide.]

At present, the EDR in CBER is the archival and functional repository for electronic

submissions and related regulatory communications. That is for the electronic submissions.

My future vision, and one that we are moving forward with is that we will be using the Electronic Document Room for all regulatory communications generated with CBER and for security mail repositories for the archiving unit, and hopefully be able to scan in documents into this particular venue, so that reviewers will have access to the information 24/7, as you would say.

This way, there is no down time waiting for information to come to their office for review by our Document Control Center. We are not waiting a day, two days, in some cases longer, to receive the information for us to be able to give you a response in your product development.

Now, this particular effort has been brought forward in accordance with the Configuration Maturity Model standard IT software development model, so that it is repeatable.

Oversight. This is where things get interesting. This is not an IT initiative. This is a CBER initiative driven by, and in service to, the reviewers.

Why do I say that? Because we have a

Joint Application Design Group. That group consists of reviewers, RPM's, and various and sundry people in different roles from every office in the Center, who give us feedback on how things should be moved forward.

From there, it moves to a Project Advisory Group. This group says yea or nay to moving a development item forward and what the importance is of it, and then from there, if there are any changes because something wasn't looked at in its fullness initially, we have a Configuration Control Board, once again managed with, full of people who are reviewers.

So, the end user, the stakeholder is responsible for the development effort. Yes, I get to bring forward the vision, but we work for this together in developing the vision.

[Slide.]

Now, what does the vision consist of? Well, the EDR is an HTML interface. For those who are uninitiated, it's a web design. This is why you can reach it from high-speed access at home, as some of our reviewers have been able to do and are presently doing, so they can review electronically without moving volumes to their residence, because

many of us are flexi-place reviewers, and they can either download the information, which they do have the option, if they don't have that kind of access, carry it home and review the information, so it is now portable.

I challenge you to move a 20-volume submission with any rapidity in a review effort. It gets very hard on the back quickly.

Now, in the background of this HTML interface, we have documentum running. We also have our operating system servers, which utilize Windows NT 4.0. Also running in the background is the Internet Information Server and Oracle. This is what sets up the system that the reviewers have the ability now to access the documents that you delivered to us for review.

So, what are the features and functions? Well, I am glad I asked me that question since you weren't going to.

[Slide.]

Well, docbases. What is the one thing that most people who are at work want to deal with? Well, they really don't want to deal with work, but they want to go ahead and do their job quickly and efficiently without interference.

To do this, we have upfront set up a quick queue, where if you know your document number, type it into the Quick Find option, readily find the document. It pulls it up for you, gives you the interface to the roadmap file or to the file structure, and you can go into it immediately.

Well, there is also a cabinet structure, so after you have gone through the secure HTML interface and logged on with your CBER password, which is the same as your network logon password. You can either go to your Reviewer Cabinet, the EDR user documents, which are SOPs and training manuals that are listed on-line.

You can go to your IND or BLA cabinet, which is at present organized by year. You can access the submission by picking a cabinet. The submissions are delineated by a tracking numbers, which are your STNs or your IND numbers.

You can then find the actual amendment you are looking for either by utilization of the roadmap file or by the CBER receipt date, which is listed with your file.

Well, we have also enhanced the functionality of this by including the product name, sponsor name, and indication with every file

that is listed by leveraging information in our BIM system, Biologics Information Management System, and RMS-BLA. So, we have a tie-in with our databases to the document repository, and the information is the same. This allows people not to be confused by disparate information in places, and from the high level, you can also download the information as you so desire.

[Slide.]

Within the IND and BLA cabinets by year, you have your STN and IND listings, you have various functions. You have your roadmap file, which is your correspondence history. Every submission that a sponsor brings forward, we replace the roadmap file, because it has no regulatory information, and it then builds us a cumulative history of every submission to the file.

At this point, it is a good time to mention the sidebar of we strongly discourage mixed media submissions. The purpose of the EDR and electronic submissions can only be enhanced further for the reviewer by once you submit an electronic document, to continue to submit all amending information as an electronic submission, so that the entirety of the submission is located on the

server through the HTML interface for the reviewer to access.

This allows us to do the job efficiently and to have all the information for your file centrally located.

In addition to that information, we have CBER Letters Folders, Meeting Summary Folder, a Review Memo Folder, Secure E-mail, and Teleconferences. In other words, we have a folder for all the major products that are available or being made by the CBER reviewers in the review process.

The intent is to put it all on-line, so that there is ready and available access to facilitate the review process and discussions with the regulated industry, because you have an available document versus, well, excuse me, I don't have the document in my office, I will have to wait two days for it, I will call you back, or let me work from my notes. This is a little bit more efficient than that.

[Slide.]

Now, to make this really work, I imagine that you are probably wondering, well, if you don't know the STN number or the IND number, how can you

find your document.

Well, we have High-Level Search categories within this repository, so you can search for groups of activities, such as all BLA's, all IND's, all IND documents as far as generated correspondence, or all BLA-generated correspondence. This will be expanded as we bring more guidance to the forefront.

So, for example, if you are looking at your BLA as a reviewer, and you don't quite reminder the STN number or you haven't made a copy of the link in My Cabinets, so that you can readily access that roadmap quickly and easily, you can search for the document by office, product name, applicant name, STN, trade name, reviewer name, submission type, submission status, cabinet year, submission date, CBER receipt date, and/or keywords. In other words, it is a pretty exhaustive set of possibilities to find the documentation.

[Slide.]

Now, the EDR Inbox. We all have a system within our offices of filing information, locating information, understanding where information is. Well, the EDR Inbox, unlike My Cabinets, my

document cabinet, which will allow the reviewer to copy a link to the item, the EDR Inbox will allow us to route electronically review documents to individual reviewers for them to review.

In other words, that large cabinet-type feature in every office, which is called a Mailbox, is emulated by the EDR Inbox, so the reviewers will know in the future rollout that this information is located in your Inbox.

If you have received an electronic document for review, this is where you look for it. This carries a link to the file or some other bit of information that tells you where you need to go to execute your functions, review functions. Now, those items were routing correspondence and notifications now.

Review Notification. I just had to digress for a second. Reviewers presently receive an e-mail every time an electronic submission is loaded. That e-mail includes, if it is not an original submission, because the BIMS database in RMS-BLA would not have the original submission information in it yet, that notification will include your sponsor name, your STN or IND number, your proposed use, your product, anything a

reviewer needs to know basically at a high level as to what this information pertains to.

In the future, when we work out our routing system, which we are presently discussing at a high level and a small group of individuals working out the paradigm, they will receive their routing forms, their administrative data entry forms, everything else they need, so that instead of filling out paper, they will fill out the electronic version of the paper form that they have been using and upon signature, it will dump that information directly into the databases. This is in development as we speak.

[Slide.]

Now, this is a picture that some of you may find interesting if you know what it is. This is or these are actual pictures of our Document Control Center, in our area that we receive submissions in on a daily basis.

This is why we are going electronic, because we have a ton of paper to manage on a daily basis. We do not receive a small amount of submissions a year, we receive well over 9,000 IND amending submissions a year to manage. It is not small amount. It breaks down to quite a large

number.

So, as a response to the electronic IND, when many of the industry sponsors that I was working with said, okay, well, we can do an electronic IND, but how do we manage the individual amending submissions. Many of them will just be a page, two pages, very difficult to burn a CD-ROM or to go through that exercise.

So, we came up with this particular delivery system.

[Slide.]

First and foremost, for the Phase II Pilot Program, that accrual is closed. For the Phase I, we are still allowing for sponsors to come forward and to set up their VPN access, so that we can receive electronic documents directly in exchange with them, so that they can be reviewed quickly.

Where does this basically pay off? At the end of the BLA discussion, for labeling discussions.

For the Phase II pilot, the scope is the delivery/receipt and archiving of regulatory documents and submissions. What we are building in an individual mechanism whereby you can e-mail us through a secure connection featuring an electronic

signature, your IND or BLA amendment.

We have already completed the alpha testing with seven industry sponsors, and they have all come through the alpha testing quite quickly and easily. It has been a smashing success. We are now pausing before we go to beta where we are now going to, in the beta test, actually receive regulatory submissions electronically, and not have a backup paper copy come forward.

This is where the electronic routing and review paradigm that we are building will also be tested. This is here and now. This is not 2004, this is what we are doing now and will be delivered by October. That is our timeline for that. Any more interest?

[Slide.]

So, how do we plan to do this? Well, it will be an e-mail, very much like a cover page, and I will get into some more of the particulars. We are going to utilize standards, the General Considerations Guidance document for electronic submissions, we are utilizing those standards.

We have presently enacted a file size limit of 4 megabytes. That is not the limit for the software, but we want to strongly discourage

anybody from thinking about delivering an application utilizing secure e-mail.

Now, you may ask why. Well, the reason why is we want you to bring forward the CD-ROM version of this or the DLT tape if it's a BLA, so that we can set up a target. So, when you bring forward the original submission, we set up the file structure within the Electronic Document Room, give you an IND or STN number, and you utilize that number in the secure e-mail delivery system, so that it is readily identifiable. You will understand why in a minute.

[Slide.]

I am going to go past that, because that is kind of uninteresting at this point.

[Slide.]

Once the message is received by CBER secure e-mail, it will be decrypted by the Messaging Management System, MMS, and routed into an exchange public folder on an exchange server, so you sent the message. In three to 10 minutes typically, that message will hit a public folder. Once that message hits a public folder, because it is associated with an IND number or a BLA number, quote, unquote "STN number," we can pull up through

RMS, BLA or BIMS, the review team names, and we will send an e-mail to the team letting them know that they have the possibility, the potential of looking at this message before it has gone through the rest of the process, which should take milliseconds if there is not a problem.

But any way you look at it, once it has been decrypted, moved forward, it is now available for the review team in a public folder. After it moves through the rest of the process, it will be archived and made available in the Electronic Document Room, in the actual folder utilizing a distinct CBER tracking number which, through a return receipt message, we will send back to you, so that when you want to discuss your submission, and you want to discuss a particular amendment to that submission, you have the tracking number that has been generated through the secure e-mail paradigm that will allow you to talk to the reviewer about the specific set of documents or responses that you have brought forward to the Center.

There is not a discussion about, well, which one is it, which amendment is it, our numbers are different than your numbers. That is all going

to be eliminated.

Now, to accomplish this, submission identifier must be in the cover page header, submissions identifier, your STN/IND number, similar to fax cover page, as you see, application I.D., subject. Those two lines must be filled out.

[Slide.]

Process. As you know, we are at the FDA, it's a regulated industry, a regulating group of industry, we are going to have a process. Every bureaucracy has one. Now, when the exchange script runs, notifications will be went to the RPM and the review team. The RPM is central to the system. Why? Because any messages going out from the Center will be coordinated through the RPM for the reviewers. This way, you only receive official Center opinion.

[Slide.]

This is a slide that basically talks about what is going to happen in the background in terms of validating the electronic signature, moving to the EDR, et cetera.

[Slide.]

What are the hardware functions for the Secure E-mail Messaging Pilot, we are utilizing an

Exchange Server 5.5, Tumbleweed MMS 4.7. We are using the MMS for encryption and decryption. We can send and receive messages, exchange public folder architecture, and pilot participants should be compliant with industry standards, x.509 certificates, SMIME.

We are also going to be using PDF for the actual signature, and CBER is going to be the signature authority. Every version of Adobe Acrobat 5 or 4 has an electronic digital signature in it, has the capability.

I am not going to discuss right now how that is going to be managed. If you do have questions in that area, I do have the lead IT person here. His name is Joseph Montgomery. If you would stand, Joe? He is in the back. Please feel free to talk to him about it. We have worked in partnership for a long time now, a very good man.

[Slide.]

Recap on the Secure E-mail Pilot Program. Reviewers will be able to access Secure E-mail through their public folder structure. Submissions will be archived in the Electronic Document Room. They will be associated with marketing applications