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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

WORKSHOP ON

THE BIOLOGICS LICENSE APPLICATION (BLA) FOR BLOOD PRODUCTS

AND

REPORTING CHANGES TO AN APPROVED APPLICATION

Monday, December 2, 1997

8:30 a.m.

National Institutes of Health

MILLER REPORTING COMPANY, INC.
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C O N T E N T S

P R O C E E D I N G S

Introduction

DR. LEE: Good morning and welcome to the Workshop on the Biologics License Application and Reporting Changes to an Approved Application for Blood and Blood Components.

[Slide]

If the various acronyms and terms shown on this slide do not mean much to you, CBER truly welcomes your attendance today and wishes that you will be thoroughly familiar with them by this afternoon. If you are familiar with them, CBER welcomes and appreciates your attendance and hopes that you will share your insights as well as your concerns with CBER towards the optimal regulation of blood components.

Today's workshop will focus only on how these terms relate to the manufacture of blood and blood components for transfusion use or for further manufacture. How these terms relate to other blood products, including plasma derivatives such as albumin, immunoglobulin preparations and clotting factor concentrates is beyond the scope of today's discussion.

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In January of 1995, CBER held a workshop for the blood components industry where the topic of licensing of

blood components intended for interstate commerce was originally discussed. The presentations at that workshop outlined CBER's criteria for evaluating an application, as well as the associated administrative procedures and requirements.

Today we shall extend the discussion by describing two CBER initiatives targeted at substantially reducing the regulatory burden on both the industry and CBER, without compromising the safety and effectiveness of blood components.

More specifically, the BLA, or biologics license application, initiative will be discussed in the morning session, to be followed by the 601.12, or changes to an approved application initiative, in the afternoon session.

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The requirement for two forms of license in obtaining the initial license and the requirement to receive CBER approval prior to implementing any change to an existing license are shown side by side on this slide that summarizes CBER's licensure mechanism as of October 7, 1997.

In obtaining the initial license, a manufacturer submits applications for two forms of license, the establishment license application, or ELA, and the product license application, or the PLA. The requirement for

submitting these applications for the two licenses is codified in Title XXI of the Code of Federal Regulations, Parts 601.1 through 601.3. These applications are evaluated concurrently and CBER's review is concluded typically within twelve months.

In making changes to an already approved or existing license, the applicant submits a supplement for which CBER approval must be received prior to implementing a proposed change. The requirement for such prior approval supplement, or PAS, applies to both establishment and product license applications. CBER's review of supplemental applications for a minor or a major change are completed typically within six or twelve months respectively.

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On October 7th, the rule for reporting changes to an approved application or changes to an existing license was revised towards the goal of reducing the regulatory burden without compromising the protection of public health. The revised rule recognizes two additional ways for reporting important changes in addition to reporting as a prior approval supplement.

Under the revised rule, a change in manufacturing that has a substantial potential for an adverse effect on the final product must continue to be reported as a prior

approval supplement. A manufacturing change that has a moderate potential, however, may now be reported as CBE30, or as a change to be effected not less than 30 days after submitting the supplemental application. In addition, a change with a minimal potential may be reported in an annual report, or AR, which will be reviewed and filed at CBER without a specific approval notice. However, incorrect categorization as AR or inadequate information in the annual report that does not allow CBER to confirm the claimed minimal potential will trigger a CBER review response.

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These additional reporting categories do not affect the current requirement for two forms of license. They simply allow an existing ELA or PLA to be more expeditiously supplemented.

Additional CBER guidance that more concretely defines the terms "substantial," "moderate" and "minimal" with respect to the potential for an adverse effect is currently being prepared to allow the optimal utilization of the revised 601.12 rule that has already been in effect since October 7th.

In addition to reducing the regulatory burden in reporting changes to an existing license, CBER is currently actively engaged in similarly reducing the regulatory burden

in obtaining the initial license. This second initiative will eliminate the requirement for the two forms of license, to be replaced with a single BLA, or a biologics license application.

The architects of this initiative view it as an opportunity to streamline the current application requirements and procedures beyond a simple consolidation of the two forms of license. Towards this end, the appropriate portions of Part 601 of the Code must be revised; a guidance which accompanies the revised rule must be prepared; and CBER's database and tracking systems must be updated.

When implemented, the BLA initiative will not affect the current rule on submitting supplemental applications. The current three ways of reporting manufacturing changes will continue to be used in filing a supplemental application but to a BLA rather than an establishment or product license application.

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Through this slide I would like to present a brief overview about how the rest of the session will go. This morning will be devoted to describing the transition from ELA and PLA to BLA, and this is a transition to be made sometime in 1998.

The components of the BLA initiative, form 356h,

and the accompanying chemistry, manufacturing and control section of the guidance document for the BLA application will be described in some detail. The supplement for making changes to the existing ELA/PLA currently active will also be applicable to making changes to the BLA application when that becomes effective.

The three components of making changes to an existing application, the prior approval supplement, the CBE30 and annual report -- these three tools under the supplemental mechanism will be discussed in the afternoon session and a specific portion for the prior approval supplement, termed CP or comparability protocol, will also be discussed in some detail. The comparability protocol is to be recognized as a tool to allow downgrading of the three reporting mechanisms under making changes on an existing license.

At this point, I would like to simply point out that this overview of the BLA of this morning's session will be described by Mary Gustafson, Director of the Division of Blood Applications, Office of Blood Research and Review, Center for Biologics. The overview of the 601.12 rule will be provided by Dr. Devine, Associate Director for Policy, Center for Biologics Evaluation and Research.

The details of how the specific initiatives relate

to the blood components industry will be discussed by members of the Blood and Plasma Branch within the Division of Blood Applications. Monica Yu will describe in detail the form 356h. Gill Conley will describe the chemistry, manufacturing and control section of the guidance document. The prior approval supplement will be described in some detail by Joanne Pryzbylik, also a member of the Blood and Plasma Branch. The changes being effected in 30 days will be described by Pat Gardner, and the annual report will be described by Judy Ciaraldi, all members of the Blood and Plasma Branch and consumer safety officers.

My name is John Lee. I am currently serving as the Chief of the Blood and Plasma Branch within the Division of Blood Applications. At this point, I would like to introduce Mary Gustafson to provide us with an overview of the BLA initiative.

Overview of the BLA Initiative

MS. GUSTAFSON: Thank you, Dr. Lee. It is good to see all of you here this morning. I think John did an excellent job of providing the structure of today's events. Also we had time and money for one workshop, so we are mixing together things that are in regulation as either final rules or proposed rules, and also proposals that we have in guidance documents which are subject to revision and

comment by everyone, and we are seeking comments.

I will try to point out to you as we go along which things are current, which things are proposed, what is regulation and what is a guidance. Hopefully, that will be sorted out. If not, be sure and ask a question so we can clarify as we go along.

[Slide]

This morning I will provide an overview of the Center for Biologics' planned transition from our traditional way of licensing biologics to a new model. Traditionally, biologics licensing involved issuing licenses for both the biological product and the establishment manufacturing the product. This licensure was based on review and approval of separate application filings, one for the product, the product license application or the PLA, and one for the establishment, the establishment license application or the ELA.

The Center is moving to eliminate the establishment filing. In the future a single application filing will result in the issuance of a single biologics license.

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As part of President Clinton's 1995 national performance review, FDA announced that it would eliminate

the establishment license application filing for a group of specified biotechnology products. FDA also committed to develop a single harmonized application form for all licensed biological products and all drug products.

[Slide]

In the Federal Register of May 14, 1996, FDA published a final rule entitled, elimination of the establishment license application for specified biotechnology and specified synthetic biological products. The rule eliminated the establishment license for the products specified in the rule. It replaced the establishment and certain other standards in the biologics regulations located in Title XXI of the Code of Federal Regulations, Part 600, with a firm's demonstrated compliance with regulations covering current good manufacturing practices. Specific information filed in the chemistry and manufacturing and control section -- abbreviated CMC section, and you will hear this a lot today -- of the harmonized application, coupled with a pre-license inspection replaced the establishment application filing. An interim application form, number 3439, was adopted for filing the BLA for the specified biotechnology products.

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The May 14, 1996 final rule covered biotechnology

products in the following categories: therapeutic DNA plasmid products, therapeutic synthetic peptide products of fewer than 40 amino acids, monoclonal antibody products for in vivo use, and therapeutic recombinant DNA-derived products. The majority of products regulated by the Office of Blood Research and Review do not fall into one of these categories -- definitely not blood and blood components, which is the topic of today's workshop. However, the spirit of the regulation and some of the specific elements of the rule do apply to the regulation of blood and blood components.

[Slide]

The May 14, 1996 rule expanded the definition of manufacturer as defined in 21 CFR 600.3(t). Unlike the previous slides that pertain only to the specified biotech. products covered under the elimination of the ELA rule, this regulatory change pertains to the manufacture of all biological products addressed in Title XXI Code of Federal Regulations, Parts 600 through 680.

Who is the manufacturer is important because the manufacturer is the party that becomes licensed. Previously the definition of manufacturer restricted its usage to one who was actually engaged in the manufacturing process. The new definition also includes any legal person or entity who

is an applicant for a license, where the applicant assumes responsibility for compliance with the applicable product and establishment standards. The expanded definition provides for much greater flexibility for the industry.

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The applicant may or may not own the facilities on which the product is manufactured. Additionally, the new definition eliminates the requirement that each contract facility engaging in significant manufacture obtain a separate license.

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The practical results of the change in definition of manufacturer are the facilitation of contract manufacturing under license, the elimination of the requirement for a separate license for the contractor, although we still intend to maintain licensing options of shared and divided manufacturing for those who prefer those licensing arrangements. It allows a product innovator to be licensed even if the innovator is not engaged in the manufacturing processes and, hopefully, it will simplify the application process.

While the May 16, 1996 final rule addressing the elimination of the establishment license and use of the interim biologics license application pertains only to the

products specifically covered by the rule, the intention to harmonize the application process between the Center for Biologics Research and Review and the Center for Drugs Research and Review for all drugs and biologics was committed to as reinventing government or EGO initiative.

[Slide]

A form 356h has been developed for this purpose. The harmonized form is in essence a cover sheet for filing an application. The meat of the application is addressed by filing attachments to the form that are addressed in a listing on a separate page of the form. The most significant for biological products are the sections that request information pertaining to the chemistry and manufacturing control for the product, and the establishment description section. It is important to note that for biological products, not covered by the May 1996 final rule, establishment standards are retained.

[Slide]

For each product category guidance documents addressing the content of the CMC and establishment description sections are being developed. This guidance is necessary before implementation of a single application filing. When appropriate guidance is available for filing the single application form manufacturers may file a single

biologics application for biological products not specifically covered in the May, 1996 final rule. As guidance is developed, its availability for comment will be published in the Federal Register. After a comment period, the final guidance will be prepared and another Federal Register announcement will advise the industry of the implementation date.

In addition to guidance for filing, we are in the process of amending the regulations that cover licensing of biological products. Currently, our regulations in 21 CFR 601 require the issuance of a product license and establishment license. Those regulations need to be revised to facilitate a single license issuance. Last, but definitely not least, the CBER licensing database must be upgraded to accommodate the new filing mechanism.

In the last few months, the Center has been busy developing CMC and establishment guidance documents for the various products regulated by the Center. The majority of the CMC documents developed by CBER follow closely the Center for Drugs Evaluation and Research's established CMC guidance documents for drug products.

The categories covered by the CMC guidance include description of drug substance and drug product, characterization of both the substance and the final

product, identification of the manufacturer or manufacturers, methods of manufacturing and packaging, validation and process controls, use of reference standards, release specifications and testing requirements, the container closure and requirements for shipping, stability protocol and environmental assessment. These categories are appropriate for most biological drug products but do not fit blood and blood components. The categories for review of drug substances are not applicable for this group of products and, if they could be made to fit, they do not offer simplification and streamlining of the application process.

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Therefore, we have taken the transition from use of the product license applications and establishment license applications as an opportunity to effect change in the licensing process. This is part of a larger overall evaluation of blood program regulation. It is an effort to optimize efforts by both the Agency and industry to ensure blood quality and safety.

[Slide]

In terms of the BLA for blood and blood components, we have considered several issues. First is the scope of the BLA. We currently license separately seven

blood component products. Each has its own application form plus the addition of supplemental application forms. The total number of application forms for blood component products licensed by the Office of Blood is ten.

We have grappled with what scope of component manufacturing should be covered within a single application. After considering several options, we have settled on the number one. That is, one application will cover a full range of transfusable and for manufacturing use components prepared by common methods within a blood establishment. For example, a new blood establishment who wishes to be licensed for whole blood, red blood cells, plasma and platelets prepared from both whole blood and by apheresis will file one biologics application that describes what is requested and how the components are prepared and controlled. In the past, such a request for licensure would require the filing of six separate applications.

We also considered the issue of facilities. With the establishment license application each separate facility was essentially individually licensed even if part of a larger license. With FDA's demands in recent years that licensees standardize operations across its license and maintain more centralized control of operations, we have been faulted by the industry for not acknowledging

industry's attempts to better standardize operations and maintain centralized control by allowing a more flexible licensing scheme.

With the elimination of the establishment license, we will no longer use the term "license location." Facilities will be evaluated within the context of a single application filing based on the extent of manufacturing occurring at the facility and the impact on safety and quality of the products prepared in that facility.

As mentioned earlier, the structure of the BLA in terms of CMC and establishment description sections applicable to other biological products are not helpful for blood and blood components. For the most part, the components are well defined. The role of licensing is to ensure that the component is safe and processed in a manner to ensure a component of consistently high quality. In addition, there are blood donor issues that crosscut the range of blood components. Our future goal is to use the licensing process to monitor the licensee's ability to maintain quality oversight of its operations.

Please listen carefully to Mr. Gil Conley's presentation later this morning as he shares with you our current thinking regarding the CMC and establishment filings under the BLA. This guidance is under development and your

input is both welcome and needed. The product that Mr. Conley will share with you today has been prepared with some input from a task group from the Coalition for Regulatory Reform. The Coalition was established nearly three years ago to communicate with the FDA concerning regulatory issues and represents all parts of the industry. We have enjoyed working with the Coalition in the past few months and look forward to working further with them after this Workshop.

In case some of you don't know who your representatives are on the task group and would like to communicate your thoughts through them, I am going to take a minute to introduce the task members. I am not sure all are here but if you are, please stand. Kay Gregory represents the American Association of Blood Banks. Hi, Kay. Steve Kassapian, in the back row, represents the American Red Cross. Ian Blomer represents America's Blood Centers. Hi, Ian. Roger Brinzer represents the American Blood Resources Association.

I will not draw on the CMC guidance longer since it will be covered extensively later. I will spend a few minutes covering some other aspects of BLA transition and related regulatory developments.

[Slide]

As part of the BLA initiative, CBER plans to

change the method we use for identifying and tracking regulatory documents. Currently, we use what is known as the reference number. It is assigned chronologically by year. Documents received in fiscal year 1997 are assigned a prefix number 97 followed by a four-digit number assigned by our computer in the order the documents were logged. A reference number is assigned to an original application or supplement without any relationship to any other number. The reference number is open as long as the submission is under review. By open, I mean it can be used to add information to a pending submission, and it closes once the submission is approved or withdrawn. After it is closed the number can be used for historical purposes to describe where information is filed but has no other relevance.

[Slide]

CBER proposes to transition to a system of logging and tracking documents that is more similar to the one used by the Center for Drugs to identify and track new drug applications. Under the proposed system, an original application will be given a specific BLA number. This number will be used to identify the application for the life of the application, which is as long as the product is licensed. Supplements and amendments to that application will be denoted by suffixes to the core BLA number. This

will result in a system that relates any and all submissions relating to an application to that application for the purpose of tracking.

[Slide]

The BLA tracking number system is not final yet but I will share with you one of the proposals. The final will most likely be close to this model. The application will be identified by an initial alpha character to identify the review center. In this example the letter "Z" denotes the Center for Biologics application. The next letter identifies the type of application. The example uses the letter "L" to denote that the application is a biologics license application. Other letters would designate other types of filings, such as "N" for new drug application, "K" for device 510(k) filing. The numbers following the two letters are the most important for tracking purposes. These core numbers identify the application. The two letters and this next set of numbers will be the identifier that will follow the application for its entire life, and will need to be remembered by the applicant and used to identify each filing. Supplements to an approved application will be identified with a suffix following a demarcation. In this example we have used a slash mark. The applicant will be advised of the supplement number in acknowledgement letters.

It will be important to remember this number as well in case additional information is sent to the file during the review of the supplement to license. Any submission to a pending file will be identified internally in the last hierarchy of numbers, the ones following the period. In most cases, however, this last group of numbers will be for CBER internal use and will not be identified in correspondence to the applicant.

The take-home message from this is that CBER will be changing the way we identify and track licensing documents. The transition will not occur at the same time as the BLA transition because we need computer enhancements that are on a longer time track. However, at some point, and hopefully within the next year, we will make the change from using the reference number to converting to a number that is specific to an application and is to be used when filing information relating to that application. For most blood and plasma establishments this will mean one number for you to remember and use in application filings. Had we not made the decision to collapse all the blood and plasma product applications into one BLA for blood and blood components, the task would have been more onerous.

When we do convert to this new system of numbering, applicants who currently hold approved

applications will be assigned the BLA number at the time they report a change to the approved application in a supplement filing. It is important to note that the application number is a separate number from the license number.

[Slide]

The application number will stay with the product even if the ownership of the licensed product changes. The license number will still definitely exist and it is tied to the applicant not the product. The license number is a four-digit number, separate from the application tracking number, and will continue in the current consecutive numbering form. It is the number that is used on the label of the licensed products from licensed manufacturers. A new applicant will be issued a new license number.

[Slide]

One of the proposed changes is that the license number will be made available to the applicant at the time the application is filed. In the past, the licensed number was issued only at the time of licensure, which resulted in problems in labeling products made during the pre-license period. It was particularly difficult for manufacturers engaged in the manufacture of frozen products. A change in the structure of the applicant, for example legal ownership,

will require a new license number. In a departure from the past, once a license number is revoked, it is gone forever and will not be reissued.

[Slide]

In another proposed change, we are considering eliminating the actual licensing certificates. That is, we propose that we will no longer issue the suitable for framing license certificates.

[Laughter]

The approval letter will serve as issuance of the license. This is consistent with the approval process for drug and device products. With downsizing of our work force, the resources expended in the actual license certificate issuance is a luxury we can no longer afford. Elimination of this process should additionally streamline the licensing process. So, I hope you can all live with the thought of not having a license certificate to hang on your wall. Elimination of the certificate issuance does require rule-making, and that is currently in process.

[Slide]

This slide is probably misplaced as I have been throwing these terms around in my presentation, but since they will be used in other presentations today I think it is appropriate that we visit some definitions. Of course, I

had to have the fatal typo some place in this presentation, and here it is. Please modify the first definition of application to read request to obtain a biologics license, not application. A supplement is a request to approve a change in an approved license application. An amendment is a submission of information to a pending license application or supplement. The entire afternoon will be spent on supplements, reporting changes to an approved application.

[Slide]

A resubmission is the submission of an application that has previously been withdrawn, or the submission of an application that was previously deficient and resulted in a "refusal to file" action by the FDA, or it is the submission of a complete response to a complete review letter. This latter type of resubmission is also an amendment to your pending application or supplement, and will generally be the majority of resubmissions filed by the blood industry.

These definitions are important to remember when filing an application, and will be covered in the next talk by Monica Yu. Please pay close attention to her presentation since much of the efficiency of switching to a harmonized form will be our ability to assign logging and tracking functions to our mail room rather than the technical staff. This change will identify regulatory

documents earlier in the document chain, and result in quicker acknowledgements of receipt, but will depend on your cooperation in providing complete and accurate information on the form.

[Slide]

So, what does all this change really mean? In the pro column we anticipate the removal of location-specific filings and the collapsing of ten applications into one to streamline the filing process for you. It also considers that blood components are usually prepared by sequential processing and are not separate stand-alone products that require separate application filings. It accommodates one filing for a change that affects multiple components and facilities.

[Slide]

Are there downsides? You bet! First and foremost, collapsing filings for multiple blood components prepared in multiple facilities under one license requires a robust tracking system. Some days I have heart palpitations thinking about it and see my federal government career flash before my eyes if our planned computer system does not live up to expectations. We could have a tracking nightmare. But I have faith in my staff who are working with excellent software developers to make this work.

The attempt to make things really easy for you in the area of filings may actually result in inappropriate bundling of supplements. It is important that only related changes be filed in a single supplement or the bundling may actually slow some approvals. We are trying to anticipate some of this and have been working with the software developers to enable additional tracking elements to enable approval of parts of a supplement should bundling of some changes slow others. But we will still need your help to keep supplement filings limited to a change or related changes.

Elimination of the ELA and location-specific licensing will do away with the licensing rollover that is common particularly in the plasma industry. Before you panic, I do think that we have additional tools, that will be discussed in the afternoon session, that will facilitate the orderly acquisition of an operating facility owned by one licensee by another licensed manufacturer.

[Slide]

I will spend a couple of minutes discussing a recent change in our regulations. Unlike most of my presentation which dealt with our proposed changes, this change is final and a current reality. On October 16, 1997 a final rule was published in the Federal Register that

revised the requirements for a responsible head for biologic establishments. This change was a reinventing government initiative in response to comments received at a public meeting, held in early 1995, where manufacturers expressed their concern that the requirement that a biologics firm name a single individual with a broad range of responsibilities is out of date and out of touch with the reality of biologics manufacturing.

In response, a proposed rule was published to eliminate the requirement for a responsible head. The only negative comments to this proposal actually came from the blood industry. Some of you wanted to retain the requirement for a responsible head. Although we have eliminated the need for one person being named with broad powers and responsibilities, we certainly do not object to a blood establishment retaining such a position if it fits within their organizational structure. However, we no longer mandate that an individual be names and approved by us as the responsible head.

[Slide]

The regulations that are affected by this change are shown in this slide. The first, 21 CFR 600.10, is the specific regulation defining a responsible head and it is being removed from the regulations, as is the third, 606.20,

a section in the blood GMPs that defines the role of the designated qualified person for unlicensed blood establishments. The middle, 21 CFR 601.2 and 601.25 are regulations covering the filing of license applications. These regulations have been modified to revise who can sign a license application and receive correspondence from the FDA.

[Slide]

21 CFR 601.2 has been revised to read; "The applicant, or the applicant's attorney, agent, or another authorized official shall sign the application." Most of you will be interested in the term "authorized official" and that will be covered by Mr. Conley.

[Slide]

Deletion of the responsible head increases flexibility within a firm by allowing designation of more than one person to represent a firm to the FDA with regard to application filings. It also more appropriately reflects the current industry practices of designating different people to perform different regulatory functions.

This concludes the overview of this morning's presentations. Once again, we invite your participation and input into our decision-making as we proceed in moving from use of the establishment and product license applications to

use of a single biologics application. Now I am proud to introduce Monica Yu, a consumer safety officer in the Blood and Plasma Branch of the Division of Blood Applications, who will guide you through the new form 356h. Thank you.

Application to Market a New Drug, Biologic or Antibiotic for Human Use: Form 356h

MS. YU: Good morning, everyone.

[Slide]

I am going to explain to you how to fill this FDA form 356h, titled, application to market a new drug, biologic, or an antibiotic drug for human use. Please note that the copy of the final rules and guidance document and BLA forms are included in your handouts.

[Slide]

Let me give you some background information. This change has come under the reinventing government initiative to harmonize the application procedure with the Center for Drug Evaluation and Research. FDA proposed to amend the biologic regulation that a manufacturer would no longer be required to submit product or establishment information on one or more of the PLA and ELA forms now used. Instead, the FDA form 356h will be implemented. Since blood and blood components are biologic products, we will refer to this form as biologic license application, or BLA, from now on.

[Slide]

Some highlights of the difference: BLA is a single filing system, that is, you can put one or more blood components in the form, versus the multiple filing system that we currently use, which required different forms for different blood components. The BLA form should be submitted with most of the submissions versus the PLA or ELA which are submitted with the initial submission.

[Slide]

Since this BLA form has been used by the drug industry, some terminology does not pertain to blood products. I would like to give the definitions for the following terms since they are used throughout the BLA form.

Applicant is any legal person or entity who has made an application to manufacture any product subject o license under the Public Health Service Act.

Manufacture is any legal person or entity engaged in the manufacture of a product subject to license under the Public Health Service Act. Manufacture also includes any legal person or entity who is an applicant for a license where an applicant assumes responsibility for compliance with the applicable product and establishment standards.

The last one is the authorized official, a person or persons appointed by the applicant to represent the

applicant to the FDA.

[Slide]

Now, let's go through the form step by step. In order to make it easy to follow, each block on this form is numbered. The space within each block is not designed to hold all the information. Please use attachments as needed.

Block number 1 -- do not write in this block. This is for FDA use only. You can find a sample of this form at Tab 3, on the last page.

Block number 2, the name of the applicant -- it can be a person or entity to whom the license will be issued.

Number 3, date of submission. Record the date of the submission being sent to the FDA.

Number 4 and 5 is the telephone and fax number of the applicant.

Number 6 is the applicant address. This is the address of the applicant. The contact address for FDA use is located on the back of this form, which may or may not be the same as this one. If you have a current U.S. license number, you can put it here also.

Number 7, authorized U.S. agent, the name and address of the person or entity to represent a non-U.S. applicant.

[Slide]

Number 8, the BLA number. If you have a BLA number, this is where you should put it.

Number 9 and 10 are not applicable to blood products.

Number 11, the blood product name as it appears on the product label. You can put more than one product name on this form.

Number 12 to 15 are not applicable to blood products.

Number 16, indication for use, for products intended for transfusion, the indication for use should be included in the circular of information submitted with the product labeling. For products intended for further manufacture, indicate either for manufacture into injectable products or for manufacture into non-injectable products.

[Slide]

Number 17, the application type. Check the box for BLA.

Number 18 and 19 are not applicable for blood products.

Number 20, type of submission. Check one box only. I will go through each one with you. The first one is original. This box is for those who do not have a

current U.S. manufacturer's license, say, a first-time applicant.

The next one is amendment to a pending application. For example, if you submit QC data, information requested by the FDA, or a submission withdrawal by the applicant.

The next one is resubmission. For example, response to an FDA complete review letter, an application for a product which was previously withdrawn by the applicant, or an application for a product which previously received a "refusal to file" action by the FDA.

[Slide]

Pre-submission, information submitted prior to the submission of a complete new application, not a common practice for the blood industry.

Annual report, this is required under 21 CFR 601.12(d), and this will be discussed in detail this afternoon.

Establishment description supplement, for example, the establishment moved from city "A" to city "B" or a change in the manufacturer's name.

The next, the efficacy supplement is not applicable to blood products.

Labeling, a new product label or revised labeling

for a licensed product -- this is a stand-alone supplement. Do not check here if labeling is part of a submission.

[Slide]

The next one is the chemistry and manufacturing and control supplement. This is for manufacturing changes under 601.12 a supplement to a BLA or an additional product. This topic, again, will be discussed in detail by the next speaker.

The last box is "other" which is for any submission not covered above.

The next block, number 21, reason for submission, you can write a brief explanation of your submission here.

Number 22, proposed marketing status. Check the box "prescription product" if it is intended for transfusion use. For further manufacture products, such as source plasma, this box is not applicable.

Number 23, the number of volumes submitted. A volume is a bound set of data, such as a notebook. Most submissions from blood manufacturers are contained in a single volume. So usually you can write 1 here, as an example.

Number 24, this application is -- check the box "paper." CBER is not yet prepared to receive electronic submissions for blood and blood components. Blood

manufacturers will be notified when electronic submissions can be used.

[Slide]

The next one, block 25, establishment information. Provide the requested information for each location included or affected by the submission. Explain which manufacturing steps or type of testing are performed at the site. Indicate if each location is currently prepared for inspection, or when it will be ready.

Since I couldn't fit all the information in that block, I am showing an example of what the attachment will look like. Attachment number 1 is an example of the manufacturing location with its name, address, registration number, telephone number, contact person and a description of the manufacturing process.

The next one is block number 26, cross references. Fill in this block only if it is applicable. It can be an FDA tracking number, such as a BLA or BLA supplement number, a previously assigned ELA or PLA reference number, a label review number of a previously approved comparability protocol.

[Slide]

On the back of the form check all the items that are contained in your application. The items that are

commonly checked are, number 1, index; 2, labeling; 3, summary; 4, the CMC section; and number 15, establishment description. Again, the next speaker will discuss these sections in detail.

[Slide]

The certification and signature section, the person who signs this document should read, understand and agree with the certification statement. This form should be signed by the applicant or an official authorized by the applicant.

The address and phone number of the person who signed this document is also put on the back of this form, here, and this is the address and the phone number which the FDA will use for future contact regarding this submission.

Lastly, it is important to remember that this form will be used like a cover sheet. We will rely heavily on the information presented for proper identification, routing and filing. Please do not hesitate to call us if you need further information in filling out this form.

[Slide]

For those who want to try out this new form, FDA will only accept it when the final guidance for the blood industry is published. You are not required to use the BLA form until the final rule is published in the Federal

Register. This form can be obtained by the fax number or through the internet, as shown here.

Thank you for your attention, and I hope you will find it quite challenging filling out this form. It is my pleasure to introduce our next speaker, Mr. Gil Conley, a consumer safety officer from the Division of Blood Applications, and he will tell you everything you want to know about BLA submissions.

Information to be Included with the BLA

MR. CONLEY: Good morning. I was chiding some of my fellow speakers over coffee this morning that I really had the safer job. This afternoon they are going to talk about the implementation of a final rule that has already been published. This morning I get to talk to you about the way we think things should be, and to invite your opinions. So, how far wrong can you go talking about that?

A little bit of housekeeping for you, in front of your folders there is a 3 X 5 card. We invite you and we encourage you to write your questions. I mention that here because I am the first one who is probably really going to confuse you today. So, when I am not clear jot your questions down on those cards. There should be a box in the back of the area, or any of us who are wearing ribbons, you can hand your cards to us. While you are at lunch we are

going to meet and go over those questions. We will try to consolidate them because we are covering a great deal of material in a single day workshop. So, it will be best if you submit your questions there so that we can prorate them and consolidate them for efficiency.

[Slide]

The use of the single biologics license application of the BLA is a new concept which has caused much discussion. Although all the plans are not yet final, I am here today to clear away some of the clouds of rumor with a discussion of facts. Now, everyone knows that given a choice of facts or a good juicy rumor what most people would prefer to line up to hear.

[Laughter]

[Slide]

Even though the rumors may be much more exciting, I will present for your consideration the Agency's current thinking on the implementation and use of the single license BLA approach for manufacturers of blood and blood components.

[Slide]

Let me draw your attention to some documents that are in your notebook. In the front pocket of your notebook you should have a copy of a draft document, with a typical

government title -- deep breath! -- "guidance for industry for the submission of chemistry, manufacturing and controls and establishment description information for human blood and blood components intended for transfusion or for further manufacture. I got it out!

This is not yet published, but should be published soon although it is on the last circulation through the Agency for review. So, there is a chance that there are some items in it that may change. I would say the shortest time frame for you to see it published with a docket number will be about a month, and if there are significant changes in our last circulation through the Agency it might be longer than that. By all means, you should keep your eyes open for it so you can comment to that particular document.

You should know that what I have to say this morning is included in that document. So, between the slides and that document there really should be minimal note-taking required for you so you can concentrate on the meaning of what I have to say instead of spending a lot of time scribbling down notes.

Now, the actual 356h form that Monica has already been over with you is included at the back of that document. it is also under Tab 12 in your notebook. In either of those locations you have both the front and back form and a

front and back sheet which are the standard instructions for that form. You are welcome to read those standard instructions but understand that this is a harmonized form that has multiple uses across both the Center for Drugs and the Center for Blood. So, there are a number of things that are not applicable.

So, the first part of the draft guidance document is the information that Monica gave you earlier, detailed information about how to fill that form out. For most of you, that will be more useful information and, hopefully, not as potentially confusing as some of the information requested in the general instructions.

The use of the BLA will be implemented in the future, and there are many steps that we are going to have to go through before the entire BLA single application licensure approach is complete.

First, there are regulations to be changed that will eliminate the requirements for ELA and PLA, the establishment license application and product license application, that you are currently so familiar with, and replace them with the single BLA. These regulation changes to implement the BLA for all biologics are in process. Consistent with the FDA's good guidance practices, even these changes will first be published as a proposed rule

and, again, you will have an opportunity to comment on them. We will not be able to fully implement the BLA until those reg. changes are published as a final rule.

Even though the BLA itself, in its full implementation, cannot be completed until those reg. changes occur, there is no reason that we can't begin to use the application form 356h. Since we are anxious to eliminate the large number of forms and the paperwork that we have been asking you to complete to streamline the system, we will be implementing the use of the form prior to implementing the full system. So, part of what I will be going over this morning will be to help you understand that process and the steps we will be going through. There will be a transition period. So, this is just some of the things that need to be done so that you can watch for them and, hopefully, understand better. There will be a draft guidance, the document that you have in your notebook, that will have to be published first. There will be an opportunity for you to comment on this draft guidance aimed at the manufacturers of human blood and blood components. There will be consideration of the comments, and there will be another publication then of a final draft.

When the draft guidance is issued, that is not an invitation to use the 356h form. Once the final guidance

document is issued, you are welcome to use the 356h form. Understand, however, that you will probably then be using that form prior to our full implementation of the BLA system. Full implementation will require the reg. changes, which will first be published as a proposed rule and then as a final rule. Internally, because we have taken on additional burdens of tracking information ourselves, we have a major software upgrade project that is in process that will have to be completed before we are prepared to handle all of the information internally that is associated with the BLA. So, we will not be issuing the final rule on all of these documents until we are prepared, and the goal is to achieve that sometime during this next year.

So, when you see the final draft of this guidance document and elect to submit a 356h form, internally we will use that information and migrate it so that we will still issue reference numbers and we will still talk to you about your establishment license application and your product license application. That is as an interim stage. So, be prepared for that transition.

So, presenting current thinking, remember that there will be opportunity, both here today and later for you in writing, to comment on these documents. I ask you to keep in mind though, and listen carefully as I talk today,

to understand the goals of what we are trying to do so that your comments and suggestions can be constructive. Understand, for example, that the 356h form as a harmonized form right now is a final form. We will not be changing that form just for the blood industry because we will have to consider how it works Center-wide, FDA-wide for those purposes. So, again, if you can couch your suggestions considering the multiple goals that we must achieve.

Also understand that as I talk today, I will be often speaking like this is a done deal because it is easier to speak in the present tense and not break out issues. But, remember, we are talking about the future.

I will also be talking often about the BLA application like it is an original application because it is easier to speak in those terms, but understand that if you are filing a supplement the same information as would be relevant to your supplement is being requested for supplements. I probably said the word "supplement" too many times. Recognize that it is the same information, only what is appropriate for your individual submission.

[Slide]

If it is worth saying once, it is worth saying twice and I think a lot of this is new enough that you need to hear it from a number of different angles and a number of

different people before it really begins to sink in. Even in our sessions preparing for this, it seemed like every time we got together we all learned something new from somebody. So, clearly, it is hard to pick it all up on the first pass.

So, this form, the 356h form, should be submitted with every submissions regarding to a licensed product. It is the cover sheet which allows FDA to properly identify and route your submission. A cover letter is not required. You may use a cover letter. In fact, a cover letter is a handy place to include some of the information we will discuss later, such as the summary of your submission, but I think you will find under the new approach that you have a great deal more flexibility to assemble your applications in a way that seems reasonable and logical to you.

There will be a significant reduction in the number of forms that you have to use. The forms that will be left will be the 356h, the cover sheet for all applications. The labels will still be accompanied by a transmittal of labels and circulars, the FDA 2567. Of course, you will continue to deal with the registration form, form FDA 2830, for registration and changes in registration sites.

The Agency is trying to reduce the required

reporting while staying true to our mission to protect the public health. So, even though when we talk this afternoon about the 601.12 changes, you will see that a lot of them are geared towards reduced reporting. But it is also true that in order to maintain a level of oversight to protect the public health, there is still a fair amount of information that needs to be submitted. What will happen now, instead of including it on standardized forms of multi-parts, a lot of that will be included as addenda to the 356h form.

[Slide]

The back of the 356h form includes a list of items which may be included in your submission. Now, the list may not be all-inclusive. There may be information that you feel is relevant to the submission that is not included in a check-off box. So, that is why you would use the "other" check-off box.

It is helpful to us that you check all that apply. As Mary alluded to earlier, we are hoping that in the future our document control center will be more and more active in some of the clerical handling of our documents, and it will be useful to them especially to try to identify the component parts that are supposed to be in the submission. In the long-run though that list does not dictate the order,

the organization or the exact content of your submission. That is up to you, and you will have to give thought to how to organize your application or your supplement for a logical and reasoned presentation that will be easy to follow and will expedite approval.

Since the content of submissions will vary greatly, an index should be included with each submission. Remember, the content is more important than the exact format as long as the format is organized and reasoned.

[Slide]

This morning we are going to look in detail at the items listed on the back of the FDA 356h form. My slides are numbered to match the numbered items on the form. First we will quickly examine all the possible information items, and I will comment regarding the applicability of each item for manufacture of blood and blood components. Then we will go back to two key submission areas, the chemistry and manufacturing controls, which we will refer to as the CMC section, and the establishment information. We will go back to those areas to discuss in more detail the information which we suggest that you include in those sections of your application.

[Slide]

As I said, an index is recommended for all

submissions. The format and organization of your submission is entirely up to you, but the submission should be logically organized and complete. Remember, we do not possess detailed knowledge of your operation, and even if we have that knowledge because of previous reviews it is easy for us to confuse your operation with some other one that we recently reviewed. So, it is important that your application leads us to the facts of how things are done at your location.

Allow me to make an analogy. Look at your submission as a jigsaw puzzle of many pieces. We recognize that the puzzle is yours to assemble and present. You should be allowed to assemble the pieces and send them to us. It is not that you only need to send us a few pieces that will fit into a partially assembled puzzle that we already have in our offices; it has to be a complete picture.

Now, an analogy is no good unless you can beat it to death so we will extend it further. Please, don't send your pieces of a submission lying loose in a box for us to put together. You need to put them together, glue them in place and then send them to us to admire and to review.

If the submission is simple, like a minor change in the label, you can provide sufficient information in a

simple format. A simple label would include maybe a cover letter, completed forms and two copies of the labels.

A complex submission, like a first-time BLA, will require more organization and structure in the presentation. Assume nothing and ask the FDA to presume nothing. Your ability to exercise good judgment about what must be included in your submission and to present it will have a lot to do with how quickly your application or supplement is approved.

[Slide]

We will discuss labeling in more detail when we get to the CMC section. Suffice it here to say that you will submit both the FDA 356h form and the form FDA 2567 even if labeling is the only thing that you are submitting for review.

[Slide]

Like a journal article has an abstract which concisely summarizes the information reported in the article, you should summarize the goal of your submission, the supporting materials included and the key issues that you have noted in your submission. This is the part that says "here's what you should be looking at in my submission; this is what we're trying to get in very concise terms."

[Slide]

The CMC section is the first of two key sections. It is a catch-all for manufacturing information. In order to consistently produce a product which is both safe and effective, manufacturers of drugs and biologics must control the chemistry, or the biology if you will, of the product through all manufacturing steps. The data included in your CMC section will be among the most important data in your submission. Because it is so important, we will come back to it and discuss it in detail later.

[Slide]

Product or samples of product are sent to the FDA only by FDA request. From your past experience, you may know that you will be asked to send actual product or product samples to the FDA. But, even in those cases, do not send product or samples until you have discussed what is being sent and the shipping arrangements with an FDA representative. Our testing labs are either on the large campus here, at NIH, or possibly even in the surrounding metropolitan area, and it is easy for samples which are not properly packaged and labeled to go astray. It is important that the shipment should be expected by the FDA. Nothing is more frustrating than to lose a sample because it wasn't handled properly.

[Slide]

This section would include the data to prove that your manufacturing methods result in a consistent product of known quality. Except for novel products, the information included in the CMC section will be sufficient to fulfill this requirement.

[Slide]

A novel product would be a completely new blood product, one that has previously not been licensed. For example, if you felt that you had data that showed that you could create a paste from a mash of pooled platelets that promoted wound healing, and you thought you were at a point where you could license this product and sell it across state lines, you would most likely have to start with an investigational new drug approach, and with FDA oversight you would perform clinical trials, collect and analyze your data, and at the time when your data was sufficient to support an application for licensure, then you would file a BLA.

The data described in items 5 through 14 would be applicable. However, for most routine blood and blood components this kind of information is very standardized and accepted for standard production and these items are not relevant to most routine blood and blood component applications.

[Slide]

The data in the establishment description is the second key area of information. For manufacturers of blood and blood components it is also a bit of a catch-all area, and we will return to this topic for a more detailed discussion.

[Slide]

The FDA's authority to debar people and firms from the drug industry comes from the generic enforcement act of 1992, often called the Debarment Act because it authorizes, and in some cases requires, the FDA to forbid people or firms convicted of certain crimes, basically crimes related to the FDA's regulation of drugs, from participating in the drug industry. Those who are debarred or convicted under the federal Food, Drug and Cosmetic Act are felonies that include submitting false data to the FDA, lying to FDA investigators, paying or accepting bribes, and selling prescription drug samples.

Each time a company, any drug company including manufacturers of blood and blood components, applies for approval of a drug it must submit to the FDA a signed statement that no debarred people worked on the application. This statement can be included in your cover letter or as a separate statement, which would be identified in your index,

and, of course, signed by one of your authorized officials. If a drug firm employs a debarred person even as a consultant or a contractor, it can be fined up to one million dollars. The person illegally working in the industry can be fined up to a quarter million dollars. Lists of debarred individuals can be obtained from the FDA's Office of Enforcement or over the internet. This is a statement that should be in your applications even now.

[Slide]

Item 17, request for field copy certification, is not applicable for manufacturers of blood and blood components.

[Slide]

The user fee cover sheet is important for applicants who pay the FDA fees under the Prescription Drug Users Fee Act, also known as PDUFA, now moving into PDUFA-2 in the newly negotiated level. Manufacturers of blood and blood components, however, are not included under PDUFA and, therefore, do not have to complete this form. At one time the FDA requested that those firms not subject to PDUFA include the form with each application, and some of you have conscientiously done so. We thank you, but since PDUFA does not include manufacturers of blood and blood components the form is not necessary for our review.

We are providing detailed information today about the BLA and encouraging public comment on our plans so that each of you can avoid the kind of trouble Mr. Ledbetter is having in this next slide.

[Slide]

In case you can't read it, he has filed an application at the bank and he is asked, "I have a question about your application. Did you really think there was a chance in the world that we would approve this?" And Mr. Ledbetter wants to know if it is a trick question.

[Laughter]

Now, I don't want to be making any phone calls back to any of you that says, "did you really think you stood a chance of having this approved?" So, hopefully, we will give you enough information so that even as we move to the BLA system it will be straightforward and simple for you.

We are going to take a brief break in a couple of minutes. During that time, I will remind you again of the cards that are in front of your folders, we want you to pen your questions there so that we have a chance to answer them in our panel discussion later. The break is only 15 minutes and I will start promptly. It is ten o'clock now. Please return to your seats at 10:15 and we will proceed with a

discussion of the CMC section and the establishment section.

[Brief recess]

MR. CONLEY: Once again, I will remind you to use your cards for your questions. You are welcome to hand those questions to anybody with a ribbon on their badge or out in the lobby area. There is a box for questions and you may drop your cards there. That would be the most expeditious way of getting things answered for you in our panel session later. I wish I could say that the pharmacy will be handing out free Tylenol for the headache we are all going to get from that drill outside, but I guess we will plow ahead anyway.

[Slide]

This is that huge title I read earlier today, the copy of which you have. It should be published soon. When it is published I will remind you to please look at that document because it may change from the one that we gave you as a workshop copy today. We were just anxious for you to have this information and to allow you to have a reference so that you didn't have to spend all day writing and then go home and try to figure this out. Hopefully, you can take time to listen and understand, and what I don't make clear you can ask in questions on your cards.

In fairness to the Coalition for Regulatory Reform

who worked through some early versions of our current thinking, and helped us to clarify exactly what we were trying to say, or maybe to understand what we were trying to say ourselves, this was not a completed polished document working with that group. It is a best effort to define our current thinking of the FDA stand of where the BLA is going to go. We had hoped to continue to meet with that group but, recognizing that this is a work in progress and that your comments are encouraged, and as Mary said earlier you are welcome to route your comments through the Coalition for Regulatory Reform if you choose, but you are also welcome to comment directly to us. I know when I was managing a large group, whenever I received something from a group I usually understood that there was a strong leader in the group and everyone else signed onto their opinion. So, all I am trying to say is that it is important to contribute individual opinions on these documents also. So, look for the publication soon.

Again, I will also remind you, to avoid confusion, that most of what I am saying today is for the future. When you send in your 356h, the real heart of the information will be putting in your own format in terms of supporting documentation.

In an effort to reduce the reporting burden on the

industry, the FDA plans to take on a greater burden ourselves for tracking and filing information that has been sent to us. If you have previously submitted information to the FDA you are not required to submit it a second time. However, your responsibility is that you will keep track of the information you have sent to the FDA along with the corresponding FDA tracking number assigned to the submission.

[Slide]

In any submission you may refer to information which was included in a previously approved submission by using that tracking number and the date of the original submission. Referenced information should be unchanged since that earlier submission. In other words, if there is a change in the information it is better that you submit it anew.

When I say tracking number, I mean any FDA number that has been assigned to a submission. That might be a reference number, a BLA supplement number, or a label review number, or a CBER tracking number. Potentially there could be another assigned number because some of our communications we track through a different number system. But if you are going to reference previously submitted information, there should be somewhere on the original

document an FDA tracking number.

For example, in the case of an annual report there will not be a tracking number communicated to you. So, if you have previously submitted information in an annual report, which we will be discussing more this afternoon, then you would reference the date of the submission of that last annual report.

Of course, you may include previously submitted information for clarity. In other words, you are not forbidden from providing information that has been submitted to the FDA in the past. I would encourage you that if you think your application is clearer by including that information, that you still do so but you set it apart and you label it as something that was previously reviewed and include our FDA tracking number. That alerts us that this is an issue that has already been examined and that it doesn't require as thorough a review by the current reviewer, and help us to understand that someone else has reviewed this within the FDA and accepted it in the past. That way, you are not caught in the trap of being re-reviewed from another angle by somebody with some other ideas, even though we will look at that information as it is appropriate and relevant to your current supplement or application.

The FDA traditionally requests a minimum of one original and two copies in each submission. However, since review committees for routine blood and blood components are typically smaller than those for other biologic products we can get by with fewer copies. So, I am going to ask you to submit one original and one copy. Clearly label the original and the copy. This is partly internal. We are so concerned about the possibility of losing an original application that our fix to that is when your application comes in the original is filed in a central filing facility and the copy of forwarded for review. Typically, we do not see the original submission until the final approval folder is being assembled. And, so you send an original, clearly labeled; a copy, clearly labeled. Knowing that we are going to be probably reviewing from the copy, if you have annotated the original with special notes -- maybe you have bracketed changes or highlighted changes from an earlier submission, then the copy should also be annotated. We may not see that original, and if you have only annotated the original it does not help us in our review. There is an exception, as always. The annual report should be submitted with an original and two copies, again clearly labeled.

Labels are also different, and we are going to cover that in detail on a later slide because there is often

confusion. Here I will say that labels should be sent detached. That is, if there is a submission that includes labeling support and other issues, there will be an original, a copy and a set of labels.

[Slide]

For now, to determine what to submit you can use the document you have always used to determine submission requirements. These documents would include the checklist from the 1995 workshop, the Code of Federal Regulations, any FDA memoranda and guidance documents that have been issued in the interim and current good manufacturing practices, both the CGMP that are encoded in the CFR and generally recognized standards accepted by the industry.

In the future, FDA plans to publish additional guidelines regarding specific information our reviewers look for in each submission. We have already had some good discussions with the Coalition for Regulatory Reform. My personal favorite format, and the one that seems at this point to be preferred in our discussions, is something like an annotated checklist. This would be a checklist of items that we look for, including a block where you could designate where in your submission the supporting documentation is found to show that you have fulfilled that particular requirement.

But there are other ways that this information could be organized. It could be organized as a monograph. It could maybe be organized in a format that we have not yet considered. When you comment on the draft guidance document as published in the next month or so, you are welcome to include any comments you have about the best format for us to provide additional guidance that will be useful to you to expedite your submission review within the FDA. So, be sure to include that information in your comments.

[Slide]

The chemistry and manufacturing controls section is one of our two critical sections. In the next few slides I am going to change the order just a little bit. I am going to talk about products first and then supporting documentation, manufacturing procedures which are common to several products, and agreements that you may have made or have made with others as part of your manufacturing process. Similarly, in your slides then, I think this next slide on products you will find a little bit out of order, but that is the only slide change.

[Slide]

Products which are outlined on this slide can be approved for manufacture as a licensed product. They include whole blood, red blood cells, plasma as a broad

category which includes plasma, fresh-frozen plasma from whole blood or by apheresis, source plasma, platelets, cryoprecipitated antihemophilic factor and source leukocytes. So the slide does not mislead anyone, source plasma, as always, can be licensed as a stand-alone product. It is not that you have to be licensed for plasma before source plasma.

Because variations exist for each product, you must carefully read your approval letters. You are approved only to manufacture the specific product described in your approval letter from the FDA. If you have any questions about the products you are licensed to produce, you should contact your CBER representative.

[Slide]

The major SOP categories we expect to review are the same as you have become accustomed to in the past. First, donor suitability, and this would include your SOP for donor deferral. Blood collection and processing, which would include arm preparation, sample collection, specimen handling and a list of tests of record performed on the products. This is just a list of tests. We do not need for you to submit your testing SOP. You should be sure that you are using FDA-licensed kits and that you are following manufacturer instructions.

Now, just by me saying do not submit does not mean that the FDA may not be interested in that information, but it will be reviewed by the field investigators during either pre-license inspections or during normal routine inspections at your location.

Third, high risk behavior questions -- be sure you include copies of any AIDS information that you provide your donors.

Fourth, donor history forms. We should have the SOP that is followed to use that donor history form, as well as copies of any informed consent information that you share with donors and, of course, the actual informed consent that is signed if it is separate from your donor history form. We will need to see that also.

Fifth, blood and blood component manufacturing -- these are the SOPs of the actual manufacturing steps for licensed products, and the SOP for any in-process controls used to assess either precursor products or final products. Sixth, quarantine and disposition of unsuitable product.

Each of you should also identify the source of your SOP. Was it internally developed? Is it from another licensed establishment? Is it from a proprietary source? Especially in the plasma industry, it is common for people to use a standard set of SOPs through an agreement that when

the owner of the SOP updates the procedure, each user of the procedure will also update it. We need to understand what agreements exist like that.

If an SOP change is a result of an FDA memorandum or a guidance, you will follow the instructions that are in the memo or the guidance for reporting changes to the FDA. In the past, that has almost always meant that within a certain number of days you should send a letter to us that you have implemented the change. The 601.12 rewrite that we will discuss this afternoon allows more options. I expect that you will more often see that you should include the date of the compliance with the guidance in your annual report which should, again, ease your reporting burden.

[Slide]

For each label you should send detached from the original and the copy, two copies of each label, one form FDA 2567, the transmittal for labels. You should also send a circular of information if it is indicated. It is indicated if it is new to you or if you have made changes to the circular since the last approved submission. So, when a new circular is published and you have put it in place, it is wise to send that circular with your identifying information to the FDA, and when it is reviewed and approved it will be assigned a label review number. That is the last

time you have to submit that circular until it is changed again. But it is wise in future submissions to refer to the label approval number that the circular was last seen by the FDA under.

The same thing with each label, if you are adding platelets pheresis locations that are using exactly the same label that has been approved in the past, you do not have to resubmit those labels again unless you have changed them. Simply refer to the label review number that was last used for an approved submission when labels were accepted by the FDA.

With all the talk of the circular, I should also mention that the circular information is not applicable to source products used for further manufacturing.

[Slide]

The procedures listed on this slide either are or potentially can be used on more than one product. Also, a given product may be subject to more than one procedure. A detailed discussion of the specific review criteria for each procedure is not appropriate today. As we mentioned at the beginning of the CMC section discussion, you should continue to use other available documents to determine what should be included in each submission but a few general recommendations can be made:

You should provide copies of your SOP for performing each procedure. You should also include related SOP. For example, if you are using a sterile connecting device as part of the procedure, that SOP should be included in your submission. You should provide copies of any QC SOP and actual QC records, such as in-process control or results of sterility testing. You should identify particular instrumentation, such as an irradiator, or particular systems, such as filters, that are used in the individual process.

Again, I remind you to read your approval letters carefully to be certain you only manufacture as a licensed product those items for which you have received written approval from CBER.

[Slide]

Manufacturing agreements, and as Mary went over with you earlier, some of the rewrites of the regs. liberalize your options for using contract manufacturing. Even though some actual manufacturing steps or activities in support of manufacturing, such as testing, are performed by people not directly under the applicant's control, the applicant still has responsibility for compliance with the applicable product and establishment standards. It is important for you to provide information on the agreements

you have made with others in support of your manufacturing. Remember, this information -- and I am going to go over it in a moment because there is a fair amount of detail -- is in that draft guidance document. You do not have to write all of this down.

So, for each contract you will summarize each contract. You need not divulge business secrets, such as fees and volume discounts that you may have negotiated. But you do need to explain the agreement with your contractor. You do not need to provide a copy of the actual contract. But we should have a detailed description of the services provided. That may be an exact list of the tests performed or a detailed explanation or even an SOP of the manufacturing steps performed. If you have agreed to product or sample shipping requirements, as you should if you are exchanging product or samples, then those should be explained.

The responsibilities of each participant in the agreement should be explained and, as part of our wanting to move to more of an understanding of your systems approach, we are going to want to know how you decided to manage the quality assurance oversight between you and the contractor. We need a list of your contractors. That will include their name, their address and their FDA registration number. If a

facility does not already have a registration number, then please include a copy of the FDA 2830 form, the registration form, that has been forwarded by that contract facility to the FDA. This is simply to alert us that there is a registration for that contractor in process in our system. It is the responsibility of the other facility to send that original form into the registration system.

Now, as soon as I start saying contracts people begin to think of all the people who do things for them in their establishment. So, to help you understand what contracts you should report and which contracts you need not report, there are a few examples. Do report in your submission an outside testing lab for test of record related to the product. Do report outside irradiation facilities. Do report product collection, such as apheresis services that you have contracted out. Off-site storage of blood and blood components; any staffing services who provide staff that is involved in the manufacturing. If you bring in phlebotomists or nurses through a staffing service, if you bring in someone that works in your component preparation area through a staffing service, then those contracts should be reported. Confirmatory testing that is used for donor reentry is a contract that should be reported, and suppliers of red blood cells for immunization.

Do not report hazardous waste disposal, equipment, maintenance and service, housekeeping, confirmatory testing used only for donor counseling, QC testing such as leukocyte counts, platelet counts and sterility testing, donor emergency treatment or donor emergency transport contracts.

Again a caveat, just because I don't want these things submitted for CBER review does not mean that a field investigator may not look at these issues because they certainly may. It may be very important to what they are looking at in your testing location.

Besides providing this detailed information, believe it or not, it is not always apparent how that contractor fits into your manufacturing organization. So, also through an outline, a diagram or a narrative you should explain exactly how a contractor or contractors are integrated into your manufacturing process.

[Slide]

If you participate in either a shared or divided manufacturing agreement, you will want to provide similar information to us. There should be a list of participating manufacturers. You should summarize in detail the terms of your agreement. Again, you need not include confidential information. Again, through an outline or a narrative you should explain how each participant is integrated into the

manufacturing process.

A little bit of an aside here, whenever I begin to talk about contracts, contractors, business arrangements, there is immediately a concern that some private business information may be released by the FDA through a Freedom of Information or an FOI request. I want to reassure you that there are strict procedures within the FDA for redacting or striking out any confidential information from documents released under FOI. FOI does not allow the release of confidential business information. So please be reassured about that.

[Slide]

Now we come to the second critical group of information, the establishment description section. Here, especially when you comment to the document, you need to understand the FDA's goal which, here, is to understand your organizational structure and function sufficient to make competent judgments about the ability to produce a quality product in conformance with the law, the regulations and good manufacturing practices.

Up until now our approach has always been through a detailed review of exactly what you do. We are recognizing that both the current thinking, and we think the good thinking about quality assurance and quality

manufacturing is moving more to a systems approach. You have all worked on this through your own QA processes to try to make sure you have control of what you are doing. Our hope is that we can gradually move from detailed item by item review to a review of the systems and how you manage them within your organization. Granted, if we have to go back and enforce a compliance action we are probably going to have to put together the same kind of detailed records we always have because that is the way the legal system is set up, but as far as routine review, the hope is to see a change. A lot of the information we are going to be asking for in your establishment section will support us as we begin to make that change. So, it is different but, again, when you make comments to the document let us know a better way to move towards our goal. We will be discussing here in the establishment section organization and personnel, physical plant and major equipment and quality assurance.

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In your submission you should summarize the general characteristics of your organization similar to an annual report of business activity. Again, do not submit confidential or proprietary information. But you should provide the kind of information your organization has probably already published in an annual report. Whether you

are for-profit or not-for-profit, you have an annual reporting mechanism to your stakeholders, and the majority of the information that I am going to mention here is the kind of information you usually include in that report because it explains your organization and how it functions. The kinds of information that would be included would be your ownership, your principal officers or business partners. What is your not-for-profit status? Are you for-profit or not-for-profit? What are the products you produce? Licensed and unlicensed?

Again, you may only refer back to your annual registration form which lists all the products you produce, but if you are into another product manufacturing area it is useful for us to know that information when we try to characterize what kind of organization you have. What are the approximate production volumes? So that we can understand if you are a small or a large manufacturer. Give us a descriptive summary of your client base. Again, I don't want a list of every client, but it is nice to understand if you are servicing yourself in a single hospital setting, or whether you are servicing multiple hospitals or across multiple states. A description of ancillary activities that you are also involved in will help us to understand your staffing relative to your

manufacturing production. Perhaps the staffing will look large but if you are also operating a centralized cross-matched service out of your facility, then that would explain your staffing issues.

Really, you should include any item which you believe will help us to understand your organization. There should be an organizational diagram. Again, this is something that a well-run organization already has on hand. The diagram should show reporting authorities and provide the names of key people with decision and oversight authority in your organization. Especially for a large blood bank, the first thought is how detailed does this have to be? Well, it is going to be a very general answer because it should be detailed enough for us to understand how work, decisions and oversight flow through your organization.

You should also be responsible in your presentation of your organizational diagram. In other words, don't be one of those organizations that says, "oh yeah, that's the organizational chart but nobody goes to George, like it says there; they all go to Mary because she knows what she's doing." Make sure that your organizational diagram reflects the way your organization really works.

Again, remember that if you have previously

submitted this information, for example, if you include an updated organizational diagram in your annual report, you do not have to resubmit it with each submission unless it has changed. You may reference the earlier submission. You don't have to do it over and over again.

Now, it is reasonable to take a moment here to remind you that there is no longer a responsible head who has assigned responsibility for the entire operation. That responsibility belongs to the applicant, the manufacturer. In other words, when you turn in your organizational diagram, whose name is at the top? If there is reasonable reason for a compliance action by the FDA, you can bet that the person culpable is considered the person at the top of your organization. This is no different than any other FDA regulated activity, and the people who are at the top of your organizational chart need to understand that. If you are a QA representative here today and you feel they don't, it would be a good idea to explain that when you go back. That is where the responsibility lies, and the organizational diagram should document that for us.

So, if you are a blood bank that is operated under a parent corporation that is a consortium of hospitals or other medical businesses, we need to know about that link as well because at the top of the organization is where the

responsibility lies. It cannot be delegated.

You should also give us a list of authorized officials. Authorized officials are those authorized by the applicant to receive and send correspondence to a BLA or a BLA supplement. That would include the name, the title, the mailing address. If their actual location is different than the mailing address, you should include a location address, a phone number and a fax number. When information is received at CBER in the form of a supplement or an application, we will review to see that someone on the authorized official list has signed the application but that is the limit of what we will check. So, if you have limited authorities assigned to your authorized officials, perhaps you want to have someone who can discuss a submission but not implement a submission -- well, those controls are entirely up to you within your organization. Those are controls that you will have to enforce. We will only check to be sure that there is an authorized official who has signed the submission.

[Slide]

Your manufacturing facility still must comply with all the requirements for the physical plant as listed in the Code of Federal Regulations, specifically in Title XXI in CFR 211's and 606's, and also any items that may be included

in current good manufacturing practices. However, since blood and blood component manufacturing is largely done in a closed system, these issues are not as critical for our reviews as in some other reviews of biologics manufacturing. So, your records will be reviewed on routine inspection or during a pre-license inspection but there is no particular physical plant information which must be included in your applications to CBER. Again, you will have to show some judgment because if you have a particular key item that relates to your physical plant, please include that information. There is much more latitude for judgment, or for you to recognize what will be important in a review and understanding of what you want to do.

Major equipment involved in the manufacture of a licensed product should be included in your submission or supplement. In a table you should list the equipment you use in the manufacturing of a particular item that you have submitted. Since for most of you that will not be original applications, it will be the specific product that you have included in your particular supplement. You should tell us the number of units, that is, the number of pieces of equipment that you are using; the model; especially if software is on board, you should let us know what version number software is in use. There should be a description of

the equipment used, and any pertinent notes about that equipment. For example, if you are using special chambers on apheresis equipment, that would be a pertinent note. The kinds of equipment that should be included includes the computer system and associated software. This is your main CPU. Apheresis equipment, blood irradiators, sterile connecting devices, infectious disease testing instrumentation, self-contained mobile collection units.

The equipment that does not need to be included in your submission would include computer peripherals, such as printers, label printers and terminals; any PC-based systems, such as word processors or spreadsheets. Any laboratory testing equipment other than infectious disease testing instrumentation need not be included, as general laboratory centrifuges need not be included, neither do refrigerators, freezers or other temperature or humidity control storage systems need to be included in your submission.

[Slide]

You should describe in detail your QA program. Now, remember, it is important that the functions of QA be performed in your institution. The FDA will not criticize your particular organizational approach as long as the goals are being accomplished consistent with QA practice.

Depending on your organization size, you may have a large QA unit or only a few people who are assigned QA duties in addition to other responsibilities. So, as I go through this section, when I say QA unit I am referring to those people in your organization responsible for QA functions.

These are the same issues which should be covered in any good QA plan. In fact, you may simply be able to submit your QA plan and the supporting SOP in order to cover these issues. Issues to be described should include the QA unit's reporting responsibility. To whom does the QA unit report? How does the QA unit fit into your overall organizational structure? What is the QA unit's manufacturing oversight? That is, which facets of the manufacturing does the QA unit have oversight? Is it internal only or does it include contract manufacturing? Does it include materials and supplies, laboratory testing? What are the authorities of your QA unit? Where do they have clear authority to act? Or, is their authority limited to reporting or to recommendations? How are they involved in personnel training and assessment? How are they involved in monitoring or conducting competency evaluation, proficiency testing, systems validation, problem investigations? How do they record them? Who is responsible for looking for trends in your problems? Who is

responsible, and how is it done to reevaluate the solution that is put in place to be sure that the solution had the desired effect?

Audits -- again, the audit structure is something that you should explain to you. Who sets them up? How are they done? When problems are identified, what kind of follow-up is your standard in your organization?

That is pretty much a summary of a BLA submission as we currently understand it. Understand that we have tried to make reasonable recommendations and set realistic expectations, but realistic expectations -- everybody has their idea of what they are.

[Slide]

I had to use this cartoon because the paper the man is handling across the four frames says, "FDA bans Phen-Fen. Panic ensues as reality sets in. Have a liposuction." The caption across is, "How are we supposed to lose weight now that Phen-Fen isn't available?" Well, there is always a low fat diet and regular exercise.

Perhaps I need to rephrase the question, how are we realistically supposed to lose weight now? Well, realistically we have tried to set standards for an application, for biologics license application in particular, and to initiate a shift in our oversight. You

need to realistically recognize what is currently being discussed versus what is pretty well set. What is pretty well set is that there will be a standard harmonized form. Right now that is the 356h form. Any form we use can be updated to improve it, but if you have recommendations you may have to consider that that is a standard form used by many people throughout the Agency and couch your recommendations accordingly.

We have to accept the fact that within FDA we, like you in all of your businesses, are trying to streamline. We are going to have a central complete database that serves the purposes for at least all of CBER, the Center for Biologics, and it will operate in a way consistent with the Center for Drugs. So, this kind of harmonization is a given. It is also a given that we are trying to streamline the process and move your applications through more quickly, without giving up thorough review and without giving up the protection of the public health that is our main charge. So, by all means, comment. Comment individually. Comment through your representatives on the Coalition for Regulatory Reform, but do comment when these documents are published.

DR. LEE: Thank you, Gil. By this point you are either thoroughly confused or elucidated, and I think we

will now break for lunch. We have about one hour. Let's promptly reconvene in one hour, at which point we will start with a panel discussion and then move to the afternoon session.

[Whereupon, at 11:00 a.m., the proceedings were recessed, to be resumed at 12:00 p.m.]

AFTERNOON SESSION

[12:00 noon]

Questions and Answer Period

DR. LEE: We will begin with the panel session of the morning session. There have been a lot of questions submitted through these cards and we will try to address the ones that are more relevant to the morning session, and save those that are more appropriate for the 601.12 rule for the afternoon. We will try to get to as many questions as possible, obviously.

We will start with question number 1. The first question is directed primarily at Mary Gustafson. Why does the blood center need to have the circular of information approved individually when the entire circular is approved by the FDA before AABB prints the circular?

MS. GUSTAFSON: We do review the revisions to the circular before the circular is printed. However, the circular of information is a manufacturer's document and even if you use a circular that is developed by, I believe, AABB, ABC and ARC, there is still information that we need. 606.121 requires that each manufacturer use a circular of information and that the circular of information be identified with the manufacturer's identification.

Also, we want to see the circular to make sure

that you are using the most recent version or revision of the circular. We do ask for just one copy though because we don't need to have stacks of circulars all over, but it is important that we get the documentation that you have personalized the circular for your institution and that you are using the right version of the circular. Also, we do have people who make modifications to the standard circular for their own use, and we want to see those modifications as well.

DR. LEE: Thank you. There is a second part to this question which is rather obvious. It simply refers to what is a circular of information for labeling, and it simply is an extension of labeling for blood and blood products that are printed to be applicable to all blood and blood components which are individually modified by each firm for transfusion products.

I will move on to the next question, and this is directed to Betsy Poindexter. At this point, I would like to introduce Betsy as a member of our panel. She is a reviewer with the Division of Hematology in the Office of Blood Research and Review, Center for Biologics Evaluation and Research.

The question is regarding products which can be licensed, are platelets and cryoprecipitated AHF considered

licensed regardless of the source, i.e., whole blood versus apheresis? It appears that cryoprecipitated is okay in this way but platelets are treated differently.

MS. POINDEXTER: Platelets and platelet apheresis are individual products for which each manufacturer in each location under manufacture should be submitted separately. For cryo. prepared from whole blood preparation, you submit the paperwork as you have in the past. We haven't required sample submission for probably ten or fifteen years. Cryoprecipitate from automated pheresis products is not currently a licensable product due to the open systems that are involved with the machinery. Platelets pheresis products prepared at each of the blood centers, with the variations in machinery that are involved and the handling of the products, require that each of the centers in each of the locations submits separate applications.

DR. LEE: I hope that adequately addresses the question. If you have further uncertainty, there will be opportunity for you to clarify your question. In fact, I may be asking you to clarify your questions as sometimes these cards are not entirely clear.

The next question is directed to Mary Gustafson again. Can a license representative visit the FDA and see or review exactly what is on file for a long-standing

license holder?

MS. GUSTAFSON: This would be a most unusual request. I am not going to say it can't be done or it has never been done, but we feel that the request would need to come under the Freedom of Information because there may be voluminous amounts of data or information that may not be filed at one site. Also, because the files contain internal review memos, as well as your submission and the approval letters, the file would need to be redacted. So, it is not a simple request. I think if there is a need -- you know, perhaps if you are new to the firm that has absolutely no records and you have absolutely no idea what you are approved to do, we would try to work with you to get the necessary information, but I think it would be quite laborious to have someone come and review the entire licensing file for someone who has been licensed for a long time.

DR. LEE: Thank you. The next question is for Mr. Conley. For questions and assistance when filling out the BLA, who is the appropriate person to contact, and what contact method should be used?

MR. CONLEY: If you are in an existing licensed location you, no doubt, have a consumer safety officer that you are used to working with. This system will not change

under the BLA. You will contact the same people for assistance. If you are a new applicant and unfamiliar with the system and not working with the CSO, the list of speakers at the bottom includes the address for the Division of Blood Applications and appropriate phone numbers that you could use to make contact with the Office.

DR. LEE: Here is another question along the same lines. Given all the proposed rules, final rules, draft guidance documents, final guidance documents etc., to be issued by the FDA, will there be a single source, such as the Federal Register, for announcing, publishing and releasing such documents, or will there be multiple sources, such as the Federal Register, CBER fax, internet etc?

MR. CONLEY: Again, you can depend on the Federal Register to be the main location that will at least announce the availability of guidance document, and will then instruct you how you can request copies. There is a sheet in the front pocket of your folder about the ways to contact the FDA, and if any of you are not net users, I would encourage you to get involved in that because through the identified web pages you can locate and search for key words on documents throughout the FDA. I will tell you that right now, even with documents on my shelf, I often find it easier to find documents through that net. If they took my net

services away I would suddenly get a lot dumber. So, I would encourage you to take advantage of that. Of course, there are representatives from a number of professional organizations that keep you updated, but all of this starts with the Federal Register. Everything will at least be announced as available there and many things will be published in the Federal Register.

DR. LEE: Thanks for the clarification. Here are two questions, basically the same question I believe, about the from 356h and its use. When can manufacturers begin voluntary use of the form 356h for submission of manufacturing and labeling supplements? What action or publication will trigger voluntary use of such form?

MR. CONLEY: This is a recap, and you can find some of the information on the slides or in the notes in the guidance document that, again, is in the front pocket of your notebook. You may begin to use the 356h for a particular product when the guidance document is published as a final guidance.

Today we only talked about the guidance document for human blood and blood components. Some of you are manufacturers of other products. In fact, for any product or product line there will be a CMC guidance document published. Again, they will all follow our good guidance

practices. They will first be published in draft, and when published in draft that is for you to review and comment, not to begin using the 356h form. When the guidance is published in final form, then you are welcome to use the 356h form. Recognize that for blood and blood components that does not mean that we are now using a fully implemented BLA system because until we have all the reg. changes in place, until we have our database ready to receive the information, we will continue to review your information and issue ELAs and PLAs, as appropriate, for the application or supplement. Once everything is in place, when you file a 356h you will then receive a BLA number that you will reference in all future submissions.

I should probably also comment that in the reg. changes, at least the early draft I saw, there is also a window that will be allowed. Once the final reg. is published, -- I think the initial recommendation but look for the final rules -- six months, recognizing that it takes a long time to put these applications together, you will be allowed to continue to submit as you always have, and we will adapt appropriately with you. In other words, you will have a six-month window before you will be required to submit a 356h and deal only with the BLA and BLA supplement approach. So, it is a large window of transition and you

will have to pay attention to the published documents to be sure you know what is going on. But there is enough flexibility built into the system that it shouldn't be a problem for any of us.

DR. LEE: Thank you. The next question is for Miss Gustafson. Will this BLA and form 356h be used in the future for those manufacturing facilities which process plasma by fractionation into plasma derivatives, or will plasma manufacturers be required to submit an ELA and PLA for each plasma product?

MS. GUSTAFSON: As a reinventing government initiative, the Agency committed to harmonize the application filing process for all drugs and biological products. Therefore, the form 356h, which you saw today, is the form that will be used for all drugs and biologics for licensure and for new drug approval.

The scope of this workshop, however, is limited to blood and blood components. CMC sections for other biological products have either been prepared or they are being prepared right now. In fact, the one for hematologic products is on a faster track than the one for blood and blood components because we didn't get as much input at the front side. It basically involves transitioning the types of information that is reviewed now into a new application

format, not changing the paradigm for review as we are trying to do with blood and components.

So, the short answer is yes, the form is going to be used for all biological products. The implementation will be on a different track, depending on the product and when the CMC guidance is available.

DR. LEE: Thank you. This appears to be a follow-up along the same lines. For those who already have the BLA and PLA, when should we need to submit all of the CMC information? Is it only when we have a need to file a supplement, or should we go ahead and file and include this information in the annual summary?

MS. GUSTAFSON: In our conversion to the BLA, we are deeming all of the approved PLAs and ELAs to be a BLA. So, therefore, you will not need to submit information as if you were filing an entire new BLA. You will submit only as required under 601.12, which we will talk about this afternoon, and in the appropriate categories, depending on whether it is a change that is likely to have a significant impact on the product, moderate or minimal. Therefore, those types of changes will be submitted in those categories, but you will never have to go back and just submit all of the information anew.

DR. LEE: Thank you. The next question is for Gil

Conley. Will the BLA format be finalized for all biologics in 1998, and can the BLA format be used even if the product is not a specified biologic or doesn't fall under biologics approved to use the BLA format? Can it be prepared if allowable?

MR. CONLEY: Probably to say again, the use of the 356h will be done at the point in time when there is a final guidance document or other documents, such as the specified biologic products that says things are in place to use it. It has to be a final document. When the BLA itself is fully implemented, that includes no longer issuing ELAs, PLAs and reference numbers but, instead, a single biologics license application. Our goal is to have everything in place by the end of '98. But one of the key issues for us is a major software development project, and you all have been through this and you know how predictable the deadlines are. So, I am not going to stand up here and promise that by the end of '98 we will be in a fully implemented BLA system because I am just not that foolish. That is our goal. If everything falls in place as planned, then BLA's will be in place by the end of '98 for all of our blood and blood manufacturing projects, and the rest of CBER is also trying to follow that goal.

DR. LEE: I hope that point is crystal clear now.

The next question, how would section 20 of the form 356h, which refers to type of submission be completed for what is currently considered a platelets pheresis supplement?

MS. POINDEXTER: Section 20 is the CMC section. Currently we are working on a draft guidance document, and until the time that that is published and commented upon and final, you would submit all of the information you currently submit as far as donor screening and testing, product preparation, labeling, quality control information -- all of the things that you currently submit will fall into the CMC sections. Gil said that the box you would check would be the CMC section, the chemistry, manufacturing and control supplement.

MR. CONLEY: I might be preempting a question that John will be able to flip through later, but it is appropriate here. There was at least one question where there was some confusion with the numbering that Monica used when she talked about how to fill in the form and the numbering that I used, which was the items that are specifically to be included on the back of the form. Because the front of the form, as it was designed, does not include numbers to define the blocks, in section 3, that is Monica's talk, in the back there is an item that is mocked up and numbered so that we could easily refer to each box.

The similar numbering is in that draft document, and it is numbered 1 through 26, and this reference, number 20 -- I don't want to get in the habit of people referring to that numbering because it is not part of the form. That was a convenience factor for today. So, if you have a question about which box to check in the type of submission box, that is where item 20 is. On the back, where they are numbered 1 through 19, it is perfectly reasonable to talk about the application contents by the numbers that are part of the form. So, don't be confused in Monica's presentation and in mine about the numbering system. Recognize that we did a numbering convenience in both the draft document and in Monica's presentation to discuss the front of the form. Those numbers are not part of the actual form.

DR. LEE: I think that is a problem that will automatically go away when someone tries to use the form. Here is a quick clarification about the form again. This may be appropriate for Mary to address. Could you clarify section 11? What impact could it have on approval if more than one product is listed as in the example?

MS. GUSTAFSON: Having more than one product listed would be an example of bundling. If it is a change that affects more than one product, it is entirely appropriate to list those products that are affected by the

change in that block. We would anticipate that it can be reviewed as a single supplement.

If somehow, you know, you are thinking one day that you might want to make a bunch of changes to a bunch of products and you fill out one form and you put multiple products down, and you have different things that are occurring with different products, this would be inappropriate bundling. It would definitely slow down the submission. We would most likely spin off some of them into separate supplements because they would have different time tracks for review and approval, most likely.

So, that was one thing I asked you this morning, to think about the change and think about in what category the reporting would be in the supplement, because it would be different categories for reporting that will be discussed this afternoon, and try to make each submission a related submission.

Yes, it is appropriate to list more than one blood component product if it is a single change that affects multiple components. It is also appropriate to list multiple facilities that are affected by a change on a single application. But just realize that these all need to be related changes in order for the submission to be reviewed efficiently.

DR. LEE: Thanks for that clarification. I think these are very important points to make sure that the applications are reviewed as expeditiously as possible. I guess the bottom line is that it would be best if you pretend that you are the reviewer and ask yourself how you would like to handle a particular problem if you were the reviewer. When still in doubt, please call any of the reviewers within the Blood and Plasma Branch, as pointed out by Mr. Conley earlier.

Here is a question that appears to be appropriate for Miss Poindexter, from the Division of Hematology. Under the new proposed licensing process, please enumerate the steps required for a blood center that is currently licensed to manufacture platelets pheresis in a main facility and to manufacture platelets pheresis in a satellite facility.

MS. POINDEXTER: The more things change, the more things stay the same. This form just eliminates some of the redundant paperwork that you were having to submit before. It does not eliminate the need to submit a supplement to the proposed BLA in the form 356h for each collection facility that will be doing platelets pheresis.

DR. LEE: The next question concerns the BLA tracking number. Regarding the BLA tracking number, if the BLA number is retained throughout the life of a product, how

are mergers, rollovers and purchases handled? Will three BLAs need to be filed for one establishment if the BLAs originated from three separate applicants from the historical standpoint?

There is a fairly elaborate looking example on the back of this card which basically refers to a merger situation when one blood component manufacturer is incorporated into another one with a separate license number. How will this be handled under the BLA initiative?

This is actually a very insightful question, and I would like to ask Mr. Conley to address this.

MR. CONLEY: I will give it a stab and Mary will reel me in if I make a mistake. The implication is that under the BLA system you might want to have a single owner and multiple BLAs. First of all, I am not sure why you would want to do that. But I am not going to say that it would be ruled out either in a merger situation because, certainly, we can have a single applicant who would file more than one BLA application, either under the same license or under separate licenses because, remember, your license number stays separate.

I would advise you, if you are in a merger situation and trying to make these kinds of decisions, that you call your CSO and discuss the information in advance,

maybe have conference calls or even an advance meeting to discuss your options and make appropriate decisions. The system is flexible enough to adapt to your needs. However, I would also think that our own desire for reasons of control and clear responsibility and authority, we would encourage you to operate under a single license under a single BLA for blood and blood components.

DR. LEE: Thanks for the clarification. That sounds like a very reasonable response. Mary, does Gil need to be reeled in?

MS. GUSTAFSON: I am not fishing today.

AUDIENCE PARTICIPANT: Could I clarify the question? As I understood it, the BLA number would remain the same although you may have a new license establishment number. Is that correct? Would you be assigning new BLA numbers?

MR. CONLEY: Let me talk a minute about the BLA system which, again, is designed for different needs. In blood and blood components we have elected, largely for the convenience of you all, to include all routine blood and blood components under a single BLA. In the rest of the biologics manufacturing world the BLA number is assigned to a uniquely developed product. We recognize that a single license holder, especially of a large manufacturing

corporation, will hold many BLAs, and that a BLA that has been approved may change hands over time. The intent is that that BLA number and that identification will stay the say for the life of that product, no matter how many times it is sold from manufacturer to manufacturer, or maybe even split in ownership to multiple manufacturers -- well, I take that back, I don't think we would be splitting. But in blood, because your BLA number represents multiple components, it becomes a more complex issue. It is unlikely that you would sell your BLA to someone else who would begin manufacturing those products for you who is not already a manufacturer in their own right.

So, where we would come from would be looking at issues of control and clear responsibility, and we would encourage you to manufacture under a single license under a single BLA. Because we have done this combination, for us and for you the license number and the BLA number is almost the same thing because you manufacture a set of routine blood and blood components that you identify with a U.S. license number on your label, and that you identify when you submit supplements and changes using a BLA number that will remain the same for you forever. So that is why it is potentially more confusing for you. So, when you understand the context of how other biologics manufacturers are using

this for products for which they can sell the manufacture of the product to somebody else, and you understand the context of how the system is set up for you all, unless you develop that unique product, and when you come in with that paste that you make from platelets, which was my example, that will be assigned a unique BLA because that is not a routine blood product. Did I make that clear or have I confused you thoroughly?

MS. GUSTAFSON: The option is available under the new paradigm for licensing for an application to transfer from one owner to another owner. In the blood and plasma arena, because these are products that are prepared similarly in many different institutions, it is highly unlikely -- and I won't say it is impossible because the option is still there, but I think it is not as likely that you are going to transfer an application. You may transfer ownership of facilities, but in those situations generally the new owner will want to assimilate all of the manufacturing methods under their current BLA. So, for the most part, although it is an option, I can't envision that it would be used extensively. However, you all seem to surprise me routinely so, you know, it may come to pass that there will be transferring of an approved BLA. I think it is less likely in the blood and plasma area than it is in

the other biological products.

MR. CONLEY: This is really key to understanding the BLA. If it is still not clear, somebody could step to the mike and ask a clarifying question, but you need to understand that or you are going to get confused about the BLA.

AUDIENCE PARTICIPANT: So, are you essentially saying that you can rollover a BLA from one establishment to another?

MR. CONLEY: The short answer is yes. The longer answer is it depends on your situation if it is appropriate or not.

DR. LEE: Thank you. Since reading these questions from the audience, in a way I am part of the audience so if I may ask a clarifying question? If a BLA is "rolled over" is it correct to assume that the old number is discarded, to be absorbed into the new BLA number for the firm into which it is absorbed?

MR. CONLEY: Again, the system for biologics in general, if you rolled over a BLA the number would stay the same. In blood, because you are probably rolling it over into an organization that is already manufacturing the same products under their own BLA, I expect our desire would be to see you manufacturing under a single BLA. But, as Mary

said, if you come up with some unique situation and a justification for maintaining two BLAs, then we would need to discuss that and work with you.

MS. GUSTAFSON: I am going to point out too that a BLA is not specific to a facility; it is specific to an applicant. So, if you sell a manufacturing facility there is no BLA to rollover at all. It belongs to the applicant at that point of time, not the facility. So, you know, that is another issue if the question is coming from firms that have multiple facilities that buy and sell facilities frequently. It would be most likely that you would want to assimilate the manufacturing facility into an existing BLA that is owned by the applicant.

DR. LEE: I think we have gone over that point quite extensively. Moving on to the next question, this one is substantially simpler. Concerning the requirement for source leukocyte licensure, the FDA memoranda refer only to buffer coats collected for further manufacture into injectable products. Is it required that a center obtain a source leukocyte license if the center will be collecting buffer coats to be sold for manufacture of non-injectable products? Mary, would you like to address that?

MS. GUSTAFSON: The key word is for manufacture, not <u>in vivo</u> or <u>in vitro</u>. If source leukocytes are being

manufactured for the purpose of further manufacturing, then they require a license.

DR. LEE: Thank you. The next question, the FDA has recently agreed to qualifying the code for the product of fresh-frozen plasma, donor retested. Is licensure of this product covered under a presently held product license for plasma, or is a license supplement required?

MS. GUSTAFSON: Someone is right on the cutting edge. We recently have assigned some codes. We have had blood establishments express interest in wanting to market a plasma product that was prepared and basically held in storage quarantine until the donor is retested at some certain interval, and then released as a plasma product when the donor is retested, with some claims for increased safety. We have not received a supplement to date for this product and, yes, indeed, it would be a supplement as long as you did want to have the labeling claim that the donor was retested.

DR. LEE: Thank you. That point is clear to me. The next one is also a fairly straightforward question. If an organization already has products licensed at six of nine sites, will the new system BLA allow automatic licensing of the three other sites, assuming SOPs are all standardized? I think Gil might answer this.

MR. CONLEY: I would not assume automatic licensure. Again, as your approval letter will state specifically the product you are approved to produce and distribute, and if the original letter names a particular manufacturing location, you are limited to that until you receive additional approval.

Now, you will need to file a supplement for those additional locations. The required supplement information will vary according to the product which we are discussing. If it is for red cells and whole blood it is going to be a fairly simple and straightforward process, assuming you are using the same SOP and processes as you have already defined at your already approved locations. If it is platelets pheresis, as Betsy outlined for you earlier, you are going to go through a similar presentation as you would now.

DR. LEE: Thank you. I guess we will hear something more about that when you go over the comparability protocol perhaps. It appears that this is relevant to that topic. So, stay tuned for further information in the afternoon presentations.

The next question is not phrased accurately for me to glean what it is supposed to mean. It reads like this: Where should the organizational chart end if the applicant is a corporation owned by another corporation? It appears

to be about the organizational chart, the content and the completeness of it if it is a corporation owned by another corporation. Mr. Conley?

MR. CONLEY: I will make some assumption about exactly what this is asking, and if I don't answer it well for the person who has submitted it, please step to the mike and ask a clarifying question.

The organization that is owned by another organization is going to have a chart of responsibilities and authority, and we regard that the person responsible for compliance with all of the rules is at the top of the top organization. So, your chart for the parent corporation may not be detailed for all of the branches of that corporation because that is not appropriate, but certainly the reporting authorities for the manufacture of blood and blood components up through the management line of the parent corporation should be shown. Any further question?

As a caveat, be sure that those people know what they own and what the FDA considers them responsible for.

AUDIENCE PARTICIPANT: Gil, just a question on that --

MR. CONLEY: Sure.

AUDIENCE PARTICIPANT: Essentially what you are saying is if we are owned by General Motors you would want

to see Robert Smith's name at the top?

MR. CONLEY: I am sorry, say it again.

AUDIENCE PARTICIPANT: As an example, if we were owned by General Motors you would want to see Robert Smith's name at the very top of the corporate general structure?

MR. CONLEY: That is right.

DR. LEE: Well, obviously the depth to which the relationship to General Motors is described should be situation specific. Is that a fair statement? Or, how deeply do you have to go into an activity that is unrelated?

MR. CONLEY: Ownership is responsibility. I don't foresee a situation where there is a parent corporation that could own a manufacture of blood and blood components and disavow ownership of the responsibility for the quality of those products to the FDA. There is just no wiggle room on that.

DR. LEE: So it should be completed with respect to its control, and/or authority and responsibility.

MR. CONLEY: You see, the applicant becomes the highest person. The manufacturer becomes the highest level of the corporation. Those are the people who are responsible. Now, what is their responsibility? They are responsible to hire and support competent people who know the business but they can't delegate the responsibility to

someone below them. The Food and Drug Act is really unique in that stance, as well as the fact that unlike other laws you don't have to show intent to have responsibility. The responsibility goes all the way to the top when you are talking about manufacturing drugs and biologics.

MS. GUSTAFSON: I might try to clarify a point. Culpability for compliance actions is somewhat separate from licensing. When it comes to filing a license application and being the applicant, in the past we have licensed the lowest corporation or the lowest entity of the corporation. In terms of the licensing, I think we would still probably stay within that paradigm. However, as Mr. Conley is mentioning, if you are a blood and plasma firm and you are owned, you know, by several layers of corporate structure and you get into a whole lot of trouble, there could be culpability at the top for some of those compliance difficulties. So, just keep that in mind. I think, for the most part, for the licensing we are interested in the units that are actively involved in the manufacturing or have responsibility for the manufacturing of the product. But in terms of legal culpability, it does go clear to the top.

MR. CONLEY: That is not to imply that it is limited to the top; it just goes all the way to the top. So, you don't get to pass that up any more than they get to

pass it down.

DR. LEE: I think the message is clear. Thank you for the clarifications. The next question is perhaps best directed to Miss Gustafson. Is the person that signs the application assumed to be an authorized person, or does the authorized person have to be specifically designated in a separate letter to the applicant? Is the current responsible head assumed to be the authorized person unless otherwise designated?

MS. GUSTAFSON: We will assume that the person who signs the 356h under the little block that has the declaration and the responsibilities is authorized to sign that application. We also will assume that the current responsible head is an authorized official unless we hear otherwise.

Now, there may be times that someone else, other than someone who signed the 356h, will want to discuss or be involved in discussions of the application. In those cases, we will request some type of written correspondence from either the person who signed the application or someone else representing the applicant that will authorize this person to discuss the application, and this is for your own protection. In terms of the roles that those people can have, that is up to your management structure. When we

enter someone as an authorized official, we will assume that they can send and receive correspondence to and from the FDA. So, look within your organization; be careful whom you authorize as an authorized official because you may have someone withdrawing your application that you really only wanted to talk on the telephone.

DR. LEE: Thank you. Here is somewhat of a housekeeping question. I will just read it out. Can or will a similar work book be provided like the 1995 workshop book without additional information? Will a hard copy of this workshop's narrative be made available? Anybody?

MS. GUSTAFSON: We have a transcriber and the transcript of the workshop will be available. I think it is ten to fifteen days after the workshop. The hard copy, the slides that we have in your notebook should be available through the Consumer and Congressional Affairs Office and perhaps on the robofax. I don't believe that we are going to get them on the web page but there is a possibility that they will be on robofax or at least can be sent to you in hard copy form.

DR. LEE: I think we still have a few more minutes so we shall proceed. It appears that all SOP changes are required to be reported. What should be submitted, entire SOPs, changes only, only SOPs deemed significant? Perhaps

Mr. Conley could address this question.

MR. CONLEY: The submission requirements have not really changed from what you are used to. It is significant SOPs, and in the lecture I went over the list of six main areas. It is on page seven of my slides, at the bottom, that we would expect to have SOPs submitted. It is preferred that for a changed SOP you will submit the new SOP with the changes highlighted and, of course, you will submit an original, a copy, both annotated, highlighted, and a cover letter to explain what the submission is all about. Now, in the future -- not now, you will submit with the 356h form and you will follow all of the guidelines that I went through. Depending on the complexity of the submission you may include an index and all of your items.

DR. LEE: Here is a small question at the bottom of the same question. Please re-explain box number 23 applicable to blood products.

MR. CONLEY: Box number 23, the number of volumes submitted. That is 23 from Monica's talk, the number that is not really a number. In the rest of biologics it is very typical with an initial license that submissions, including clinical data, are quite large. So, we may receive an original copy that could have twenty volumes of data or more. That would be twenty three-ring binders of data.

That is a volume. Very few of you, thank goodness, submit submissions that large but, again, this is a tracking tool. Let us know how many volumes of data we are supposed to have so that when our document control center receives them, if they appear to be missing volumes they can follow up with the shipper or with you to run them down. So, most often your submissions are a single volume and that is what I expect most of yours would be. But if your original has three notebooks in it and there is a copy with three notebooks in it, you would report three volumes in that box.

DR. LEE: If a submission cross-references a product which at a later date is discontinued, does this impact that submission? I assume that the submission was active when it was cross-referenced and then, subsequent to that, the original cross-referenced submission was discontinued.

MR. CONLEY: You are always afraid that the FDA is going to play "gotcha." Our files, especially in the future when we move to the BLA system, will be clearly tracked and kept together. So, if you included facility information in a first application for a product and later referenced that facility application for product number two, and then five years later stopped manufacturing product number one, that will not make the information you referenced go away. The

reference is still legitimate. We are not trying to get you.

DR. LEE: Sounds very reasonable. Thank you. there are two additional quick questions here. This one may perhaps be best answered by Mary. Will a BLA ever be applied to albumin clotting factor concentrates and so forth? If so, when?

MS. GUSTAFSON: I think I answered a similar question very early in the question and answer period but, yes, the BLA will be applicable to all the biological products that roll out of the implementation. The BLA will be dependent on the CMC guidance document being in a final form and being ready for use. We actually anticipate that for the hematologic products, which is the question stated, that that will occur before the blood and blood components roll out.

DR. LEE: Once again, just because this workshop is targeted at the blood components industry doesn't mean that information presented here is not applicable. They could share similar types of information. However, we would like to make clear is that what we talk about is blood components and some of it might be transferrable and some of it might not be.

Two additional quick questions, can an authorized

U.S. agent be for an applicant and not just for a foreign manufacturer? Mary?

MS. GUSTAFSON: The authorized U.S. agent is a requirement in the investigational new drug regulations, which are in Part 314 of the Code of Federal Regulations. These regulations apply through the clinical testing phase of drugs and biological products. Like I said, it is a requirement. A foreign firm has to have a U.S. agent under the IND regulations. Under the licensure it is an option. If the foreign firm chooses to have a U.S. agent you would list it on the block on the front of the form, but it is not a requirement at the BLA stage.

DR. LEE: Thank you. The last question is for Mr. Conley. Is fibrin sealant subject to PDUFA payments? Although this has the name of Conley written here, we will redirect it.

MS. GUSTAFSON: A loaded question. Pooled fibrin sealant products that are derivative products are subject to PDUFA. Should someone come in with a single donor fibrin glue product, which no one seems to ever be willing to do, although we know it is out there, it would be considered a component and unlikely to be under PDUFA at this time.

DR. LEE: Thank you. There are a few additional questions but I think those are best addressed at the end of

the afternoon session, at its panel discussion section. At this point, if there are any verbal questions that can be handled in about a minute or two, we would like to entertain them. If not, we would like to proceed to the afternoon session. Hearing none, I would like to first show an overhead.

[Slide]

We began today's discussion with basically two specific goals with respective to two specific initiatives, to make a series of CBER presentations, and to receive meaningful comments from industry after the sharing of information.

We have addressed the issue of biologics license applications in the morning. We discussed the transfer of the current ELA and PLA to the BLA. In the afternoon session we would like to turn our attention to the second major initiative, which is already in effect, which has resulted in a revised 21 CFR 601.12 rule as of October 7th. It is hoped that through these two initiatives we can continue to reduce the reporting burden without compromising product safety or efficacy.

[Slide]

I put this slide up again to emphasize the fact that what is to follow in this afternoon's session is a

close description, a step-by-step description of the current procedures and requirements for making changes to an existing, already approved application.

We shall describe the initiative from a broad overview standpoint, and that description will be provided by Dr. Rebecca Devine, Associate Director for Policy, Center for Biologics Evaluation and Research. This discussion will be followed in succession by discussions of the prior approval supplement, changes to be effected in 30-days and annual report, to be given by Joanne Pryzbylik, Pat Gardner and Judy Ciaraldi, in that order, all members of the Blood and Plasma Branch. As a last topic, the issue of comparability protocols, how it relates to the prior approval supplement and how it can, in specific instances, downgrade a particular supplement from one category to the next, most typically probably one reporting level, will be described further Mary Gustafson.

At this point, I would like to welcome Dr. Devine.

Manufacturing Changes: CBER's Latest Guidance

DR. DEVINE: I thought it was very nice of them to mark the steps so I would know where to walk up without tripping.

First of all, I would like to welcome you this afternoon but I would also like to take a moment to thank

the Division of Blood Applications for all the hard work and time and effort they have put into putting on this workshop. I think it is a very confusing time for us and for you as we now transition from our old types of applications to the new ones, and I think workshops like this are very helpful for you and for us because they surface a lot of issues that we don't necessarily think about as we are developing the procedures. So, it is nice to hear from you and then we know, as we are going along, whether we are on the right track or not. So, again, thanks to Mary and Gil and all the efforts of the people in DBA for putting this on, and thank you for attending. I think it is important that we have such a good turnout.

[Slide]

I would like to turn now to our topic for this afternoon, manufacturing changes. I am going to give, as John said, a general overview, and some of you may have heard this at different presentations that I have given before but this is also for the benefit of those who have not been able to attend those. For those of you who have heard this, I apologize. You can do a little bit of daydream until we get to the more specific topics.

[Slide]

I am going to cover an update on the new

publications. I will go over the scope of the new rule and the guidance documents. I will discuss the rule in a general sense and some special features of the rule. I will briefly touch on labeling and I will try to summarize for you what the new reg. means for us.

[Slide]

The regulation that we are talking about is Title XXI Code of Federal Regulations 601.12. It used to be called changes to be reported and now it is called changes to an approved application. So, we have clarified that this is applying only to products that are already approved and not to pending applications, which would be covered under just the normal pre-approval procedures. We did ask for comment in the proposed rule as to whether or not we should have specific reporting requirements for pending applications, and the comments that we got back seemed to indicate that those were pretty well handled with the amendment process as people currently have been using for approvals.

[Slide]

The rules were published in the proposed form in January of 1996. The final rule and guidance document was issued July 24, and became effective on October 7 of 1997.

[Slide]

The guidance document which would be applicable to the blood and blood products is called changes to an approved application: biological products. There is a companion document which applies to the specified biotechnology products that are currently now using the BLA, and it is a separate document.

We received comments since publication of this final guidance document from the blood industry that they would prefer, in fact, a separate document for blood and blood components. That is currently something that we are considering adopting at this stage. So, we are looking at this guidance as possibly something that needs to be changed. So, we would provide specific guidance for blood and blood components.

[Slide]

Again, I will cover the scope of the rule. The first stage of our reinventing government initiative covered only the non-blood and blood component products that CBER regulates, and that was in the form of a guidance document that was issued in April of 1995, I believe -- yes, it was 1995. Blood and blood components were not covered by that. So, there was no regulatory relief until we got to the rule-making stage for blood and blood components. The final rule now covers all biological products, including the

specified biotech. products that are listed in 601.2, drug products that are biotechnology derived that are regulated by the Center for Drugs Evaluation and Research, blood and blood components, vaccines, allogenic products, all of our other miscellaneous types of biologicals, and it also now covers labeling, which the original guidance document did not cover.

I would just like to just briefly mention the effect of the new FDA Modernization Act which was signed into law on November 21 of 1997, as you all may have heard. There is a section in that law which deals with manufacturing changes for drugs and biological products. It is our feeling that minimal changes to our regulation will need to be made because of the new law. This was because we had a unique opportunity to know what was going on with the drafting of the legislation and were able to anticipate what the final outcome might be. So, we did tailor the regulation to some extent with the expectations for the legislative initiative. So, I don't think there will be too many changes for the biological products that will need to be made. There may need to be some clarifications that might deal with the new law and the way it is written and, depending on what the Center for Drug Evaluation and Research finds during its open comment period on their

rule-making which they have to undertake as a part of implementing the new law, we may get more suggestions or comments that might cause us to want to go back and make some changes to the regulation itself but we don't really anticipate them to be major. CBER has pretty much accepted the framework of the rule and how it is working. So, I don't think it is going to be a problem.

[Slide]

Now I am going to go into some detail on the rule itself. I just wanted to highlight and let you know, in case you hadn't noticed, that there were some changes from what was in the proposed rule in the three categories versus what ended up in the final rule. In the proposed rule we had a supplement with prior approval required, a thirty-day notification which is not a supplement, and an annual report.

[Slide]

The final rule has the three categories, prior approval supplement, thirty-day supplement changes being effected, which we now call a CBE or a thirty-day CBE, and the annual report.

[Slide]

I will discuss briefly what might go into the three categories, but the specifics about each of the

categories for blood and blood components will be discussed. Within the overall framework of the 601.12 rule, it states that the applicant will inform FDA of changes made in the manufacture, personnel, equipment and processing for biological products, and that the validation must be done before the product is distributed. This very much mirrors the law in that the validation is an underlying requirement for implementing any change to a manufacturing process in the new law.

There also has to be a demonstration of a lack of adverse effects on the identity, strength, quality, purity and potency of the product. So, even though the reporting category might be reduced, the expectations for the quality and the testing and validation have not been diminished by this rule-making and, in fact, even though some of this might be worked out during your inspection it will still be very important that you have proper documentation so that you don't end up with that on a 43.

[Slide]

Lack of adverse effect is shown by appropriate validation and/or clinical or non-clinical laboratory studies. These are covering, again, all of the biological products. So, in some cases when you make a major change it may be necessary to go back and look at clinical studies for

blood and blood components. Meeting some of the criteria and additional standards might be something you would show through non-clinical laboratory type studies.

[Slide]

The changes being affected in 30 days is the new provision which is similar to what we have in our guidance document, but published in '96, and it states that products may be distributed 30-days after FDA receives the supplement.

Now, receiving the supplement -- you want to make sure you send it in, in a manner where you will be assured that we receive it because we will not be telling you in a letter whether or not we have gotten it on a particular date. We will be sending you the reference number assignment letter which acknowledges receipt, and you might get a filing letter for the supplement, but you want to be sure that you take on the responsibility of making sure you know what day it was received by us.

The 30-days, I would like to emphasize, is not for us to review the supplement. The purpose of the 30-days is for us to ensure that you have gotten the proper categorization for the change and that you have submitted all of the required information that is specified for the supplement. Now, one of the special provisions that we

provided for is that there may be certain situations where we would waive the thirty-day wait, and I will talk about those in a few minutes.

[Slide]

The contents of the supplement, both the prior approval supplement and the changes being effected supplement are listed in the regulation, and they are also on this slide: A detailed description of the change, all of the products involved. This is one of the areas where on the form you would be specifying, as Mary said, for related changes what products might be affected; the manufacturing sites or area. This may relate to new sites or facilities, or existing sites that have had changes made to them. The methods used and studies performed to show that there is no adverse effect and that you have validated the process. We would expect data from the studies to be included, the validation protocol and validation data, and a list of relevant SOPs related to the demonstration of the lack of adverse effect. Related SOPs which are also related to the process changes would also be listed in the supplement.

[Slide]

The annual report has been a category set up for what we would be calling minor changes, which have a minimal potential to have an adverse effect on the safety, purity,

potency, identity and strength of the product. Some of these are listed here. We will go into more detail for the blood and blood components during an individual talk, but I want to emphasize here the three categories are set up based on risk of an adverse effect for the change, with the prior approval supplement being those types of changes which have a substantial potential; the thirty-day supplement those which have a moderate potential to have an adverse effect; and the annual report for those with minimal potential.

Again, we would expect all of the documentation of the demonstration of a lack of adverse effect to be on site. Some of the data will go in the annual report submission itself, and this is something that we will try to clarify more in the individual discussions.

[Slide]

We have also provided for the annual report -- since we currently have the PLA and ELA system, we have anticipated that for blood and blood products it would be rather onerous to have to do an individual annual report for each of the blood and blood components where a lot of the information might simply be repetitive. So, we provided in the rule for a provision that would allow you to ask for an alternative date for submission of the annual report, and this should come in the form of a written request. One

might consider combining annual reports for multiple approval applications into a single submission for us to review, and I think for blood and blood components this might be an appropriate mechanism.

[Slide]

The contents of the annual report are a list of all products involved; a full description of the manufacturing and control changes, including the date the changes were made, the cross-reference to the relevant standard operating procedures and validation protocols, the manufacturing sites affected, and relevant data -- the regulation actually says relevant data that would be appropriate to demonstrating the fact that the change did not have an adverse effect.

[Slide]

I would like to talk for a few minutes about some of the special features of the regulation which, we think, have made it very unique and flexible.

These are the 30-day waiver comparability protocol use of the guidance documents for listing some of the changes for the different categories. A section we are calling failure to comply, and briefly we will discuss how the implementation has been happening.

[Slide]

Waiver of the 30 days is possible under 601.12(c)(5) based on several circumstances, and most of these have been left up to the Agency's discretion in the rule. Based on our experience at FDA with the change is that it has usually been complete when submitted by companies, and companies have generally been able to get the right category. We felt that those types of changes would be possible to waive the 30 days because, as you recall, the 30 days is really to determine only that the application supplement is complete and that it has been put into the appropriate category. Similarity to a change which is a change that is being affected, a change that we already know about -- and most of these will end up being listed in the guidance documents. We don't really anticipate that these would be done individually with companies making a request on a case by case basis. So, we have already outlined some of these in our current final documents that are available.

[Slide]

The comparability protocol could be another way that one might use to waive the 30 days, and this I would see being done more on an individualized basis when you have bumped from a higher category to a CBE category and you say we would also like to waive the 30 days as we bump it down. Mary will talk more about that later.

The comparability protocol -- you will not see that word mentioned in the regulation itself; you will see it in the preamble. What we have talked about in the regulation is one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved for specified types of manufacturing changes.

[Slide]

The purpose of the comparability protocol, as it was envisioned, was for it to be a prior approval supplement that could be submitted to us and reviewed ahead of time as a mechanism for reducing the reporting category for change. We felt that if we could know ahead of time what tests and acceptance criteria the company would put forth in order to accept a change, that would reduce the risk for an adverse effect on the identity, strength, quality, purity or potency of the product. By collaboration between the FDA and the company, we could be assured that the proper tests that we felt and you felt were appropriate and adequate would have been performed before the product is distributed so that we wouldn't be put into a situation of having product distributed that we might later find to be unacceptable, and be put in a situation of a possible market withdrawal or recall situation.

[Slide]

One of the other provisions that we are very pleased with is the use of guidance documents to be able to articulate more clearly some of the specifics. Within the framework of the regulation we used terms of art substantial, moderate and minimal and the major and minor words have also been used. These were put in place so that we could provide interpretations of what we thought were changes that were substantial, moderate and minimal. But it also gave the flexibility if things were not specifically listed in the regulation for things to be bumped down; for things to be bumped up if it was appropriate; and the binding nature of the regulation would not allow you to do that. By using the term of art and providing guidance documents to get the specifics, we do allow the flexibility while still giving some predictability for people who are trying to decide what category the change falls in.

Reminders about the guidance documents are that they are non-binding. That means that if in your particular situation you feel that what is listed in the document is inappropriate and that a more appropriate proposal could be put forth by you with adequate scientific rationale, we would consider whether or not that might be appropriate for your particular situation.

The guidance documents are intended to provide

examples. They are, hopefully, to be continually updated as we gain experience with the new regulation, and this is where you can be very helpful to us. If you think that there are examples that we should be listing or more guidance that we should be providing, then please let us know. The dockets for these final documents are always open to accept comments.

They are not all-inclusive because we really could not think of every situation and every possible change as we were preparing these. So, there will be situations where something you might want to do will not be listed in the document. Again, we think these provide us with some predictability while allowing a certain amount of flexibility.

That might leave you in a situation of wondering, well, what do you I do if my change is not in one of the lists, it is not in the regulation, it is not in the guidance document? What do I do? How do I know? We feel that as companies you probably know an awful lot about your product. We might know some things about product classes that you might know that we have gained information from reviewing a multitude of applications. So, again, it is something where we need to work together to try to come to the appropriate category.

[Slide]

You would look at the level of knowledge of the product and its active components, in the realm of possibilities in biological products this would go from the very-well characterized to products that are pretty much a gemish, a mixture of unknowns, of components that might be defined more by the process rather than by an analytical test. The type of change that you are making could have potential to put it in a higher or lower category, if it is a major type of change to the process where you are really overhauling what you are doing or if you are just tweaking the process. The type of product, as I mentioned, well characterized or not, defined by the process or defined by analytical testing. Your ability to assess the impact of a change on a product and its safety, purity and potency.

The general rule of thumb is if you are not sure, then ask for specific guidance for your specific situation. As Gil mentioned earlier, there are CSOs and reviewers in each of the product offices that will be available to provide guidance for you if you are not sure where a particular change might fall and, again, proposed changes to the guidance that you think might help clarify for others and for yourself where a change might fall in categorization.

[Slide]

Another provision in there, failure to comply, 601.12(g) says that in addition to other remedies available, repeated failure to comply with 601.12 may cause FDA to require a supplement for any proposed change, and it would require approval prior to distribution of the product. This was something that we put in place because we were in a mode of down-regulating and streamlining where we thought if companies were not being compliant with, say, reporting things that should have been prior-approval supplements or CBEs and they were, say, reporting them in an annual report or not reporting them at all, that there really needed to be some mechanism to be able to bring such firms into compliance. So, we don't anticipate that we will use this much but, given the fact that it is there, I think it can sometimes have an effect on whether or not people are more diligent, if you will, about reporting and making sure they understand the rules.

[Slide]

Implementation was 75 days from the date of publication. So, that began on October 7, 1997. For the annual report, those are to be submitted within 60 days of the first anniversary of the approval of the application falling six months after publication. We did give you kind

of a little bit of a leeway, six months for those who might have an anniversary date falling within the first six months of publication of the rule. Again, as I mentioned earlier, some people can request to have alternate dates for filing annual reports.

For pending supplements we state that the firm should notify FDA which category it believes a pending supplement now fits. For example, if you have a pending supplement that you think now falls into the CBE category, whereas before it was awaiting approval, you can tell us in writing that you feel it now falls into the CBE30 category and within 30 days we will notify you if we are not in agreement with that categorization. So, for those of you who have not considered this, this is an option for any pending supplements that you might have currently with us now.

[Slide]

Again, I mentioned this is supposed to be burden reducing so let me try and explain where we are with the numbers. We estimated in our paperwork proposal that there was approximately 10,000 hours a year reduction. That is not necessarily our time but that is your and our time combined. In the fiscal year 1996, we received approximately 1,400 supplements, in 1997 1,284 were

received. So we are in a downward trend. We anticipate this to drop even more drastically once the BLA is implemented because you will be now collapsing what might have been separate supplements into single combined or bundled supplements that might be related for the BLAs in the future. So, we do anticipate a lot more burden reduction here.

Now, where the numbers will fall we are not quite sure. One of the things that might generate more supplements could be the use of the comparability protocol. So, for some short period we might see a surge of those and then a downward trend again. We will have to kind of wait and see where the numbers go, but we do anticipate an overall continued net burden reduction.

[Slide]

I will just talk briefly about labeling and then I will go ahead and summarize. For labeling changes the three categories are slightly different. They are prior approval supplement, the changes being effected supplement. There is no 30-day wait on those. Then there is the annual report. These are now completely harmonized with what appears in 314 regulations for the Center for Drugs, and are now able to have more or minor editorial changes and changes which might affect the safer use of the product to be implemented more

quickly. Again, this we think will have a benefit for the public health, not a detriment.

[Slide]

Advertising and promotional labeling is to be submitted to CBER in accordance with 314.81(b)(3)(i), which says specimens shall be submitted at the time of initial dissemination and initial publication using our FDA form 2567 or an equivalent. The reason we put that in is because we are currently in the process of revising the form FDA 2253 to begin now using it for both drug and biologic advertising and promotional labeling submissions. So, when that form has gone through its final clearance procedures, that will be the preferred form for people to use for their advertising and promotional labeling.

[Slide]

I will summarize now and then I will turn it over to others for the more detailed discussion of the three categories. So, in summary, the new rule became effective on October 7, 1997. We are now accepting supplements under the new rule. We anticipate a substantial burden reduction. We look forward to continually updating the documents, possibly even further rule-making in the future depending on what is happening with the Center for Drug Evaluation and Research and with our legal review of the new law, currently

signed into law just about two weeks ago.

There will be further guidance coming on comparability protocols, not only for blood and blood components but for other biological products as well. Again, we think we are anticipating more specific guidance on reporting changes for blood and blood components.

Let me go ahead and introduce Joanne and let her talk about major changes to an approved application and hear more specifics. Thank you very much.

DR. LEE: I would just like to make one comment on the topic of 601.12. The rule is already in effect. Your comments about this are extremely important. We are in the process of preparing a guidance document more specific for the blood components industry than the one that is currently available now. So, your comments here are just as important as the comments for the BLA.

Secondly, staff members should be circulating the aisles to collect cards. At this point, you should try to submit your questions as quickly as possible since the day is getting short. We will proceed with Joanne with her discussion.

Major Changes to an Approved Application - 21 CFR 601.12(b)

MS. PRYZBYLIK: Good afternoon. We are here this afternoon to discuss change that is in effect now. We have

our change. But this is what I am going to talk about, the major change.

On October 7, 1997, just eight weeks ago, the rule in Title XXI of the Code of Federal Regulations 601.12 was revised, and the title changed from changes to be reported to changes to an approved application.

[Slide]

That is me, Joanne Pryzbylik.

[Slide]

I will talk about the second paragraph in the revised rule, and I am sure you already have the rule memorized, 601.12(b), major changes requiring prior approval.

First, what is a major change, and the new information that will be added to the reference number assignment filing letter; the contents required for prior-approval supplement; manufacturing changes that require a prior approval and, finally, labeling changes that require prior approval. Then I will summarize.

[Slide]

What is a major change? It is a change in blood product manufacturing that has substantial potential for causing an adverse effect on the identity and strength of a product, the quality and purity characteristics of a product

and, finally, the potency of the product as measured by therapeutic activity of laboratory and testing controls.

This is the most restrictive category and requires prior approval before the product is distributed using this change. The change may not become effective until your approval letter is received from the director of CBER. CBER's new name for this category is prior approval supplement, and I will call it a PAS.

The risk potential for a particular change to adversely affect a product's safety, purity, potency and effectiveness may differ for different products. You, as the applicant, must assess the risk.

[Slide]

We are all in transition, and in this period for new submissions we will evaluate your chosen category and notify you in the reference number assignment letter if we agree with your choice, we need more information, or disagree with the category choice. Please read these letters for possible request for more information or recommendation to submit an application to a higher category.

If we agree with your chosen category there will be no comment. No news is good news. We may agree with your category but we need additional information. We might

need additional QC data or additional standard operating procedure, SOP, and this information is due to CBER 45 days from the date on your reference number assignment letter. If the information is not received in 45 days there will be grounds for a refusal to file decision.

If we disagree with your choice, for example if you request a lower category for a change that we consider major, for example you request for a change to be effective in 30 days and it should really be a prior approval, we will send you notification within 30 days from the date we received your submission to elevate your change to a prior approval supplement, and we might ask for additional information at that time.

If the submission belongs in a lower category in this transition period, for example you submit for a PAS and it belongs in maybe changes to be effected in 30 days, we will review it as usual but the approval letter will state that this particular change belongs in a lower category for future submissions.

[Slide]

I would like to thank Dr. Devine for this slide. I just thing it is wonderful. 600.3 was amended to clarify the definitions for amendments in supplement submissions. It is a great slide and I want to give you an example of

each.

An amendment is the submission of information to a pending license application or supplement, and it is to revise or modify the application that was originally submitted. So, this is something pending. An example of this would be that we received a request for a single platelets pheresis and maybe within a week you decide you would like doubles also. You may submit that as an amendment as long as it is at the same location, using the same equipment.

The supplement is a request to CBER, to our director, to approve a change in an approved license application. An example of this would be that you already have a product license for the primary product or component. It could be red cells, platelets or platelets pheresis. This request would be to modify the product by maybe leukoreduction or irradiation.

[Slide]

In our experience, these major changes may cause detrimental effects on the safety, purity, potency and effectiveness of the changed product even when an applicant performs thorough validation or other studies on the product or the production process, or both.

A PAS is required for a major change in the

product. For example, you already have an approved license for both platelets and platelets pheresis and now you want to manufacture them as leukoreduced products using a new filter or apheresis instrument.

A major change in the production process, and the process starts when the donor history is initiated and progresses to the final product's storage and distribution.

If you substantially change your quality control procedure to measure product quality, it is extremely important to monitor its progress. An example of this would be using a new procedure or method to count leukocytes for leukoreduced products. Please note that FDA still requires sending apheresis products for QC for platelet products as part of the submission approval, and also for leukoreduced platelet pheresis submissions.

Finally, major change in equipment, an example of this would be new apheresis machines or other new equipment used to change the primary product or component.

Also, major labeling changes that have an impact on your final product, they are also considered major changes.

[Slide]

These seven items are the minimum amount of information that is needed in the supplement for a changed

product. Just like the information needed for a great newspaper article -- "what, who, where," how and we will provide the "when" when your product is approved.

I will first describe the product for the proposed change in detail and in specific language for the product.

Where will it be manufactured? Tell us where the product will be manufactured, at the main facility or at one of your other facilities, or both.

How will you do it? Give us a brief description of the methods used and the type of studies performed. For example, a new method to leukoreduce platelets and a brief summary of the results of the test runs.

Submit the data from the studies. This is an important part of the submission to ensure potency and purity in the final product. For example, for your leukoreduced platelets pheresis, after you have filtered it the residual leukocyte count must be less than 5 times 10^6 leukocytes per container, and there must be an 85% retention rate for the final platelet product.

Validation should be part of the prior approval contents, and this is necessary to assure that the instrument or process change is performing according to the manufacturer's claims. For example, in an apheresis product data should be generated for each different type of product

manufactured, each instrument model and, finally, for apheresis software that has been substantially changed.

New or revised SOPs to the product require prior approval, and a list of the relevant SOPs will be covered a few slides down the road. Again, new and revised label changes also require prior approval.

[Slide]

On July 24, 1997 the guidance for industry for changes to an approved application was published. Of the many major changes that were listed, only a few directly apply to the blood and plasma industry. Right now, the Blood and Plasma Branch in the Division of Blood Applications is developing a specific guidance document for the blood and plasma industry.

Processing changes that we are interested in are new and revised recovery procedures. The product examples are on the next slide.

Also a change in the processing steps, which include adding, deleting steps, are also important if it directly affects the product to improve product safety, quality and consistency. This is an important change and we would consider this reportable to us.

A change in the solutions used in blood product collection is also reportable to us. If you are now

collecting the standard 450 ml units of whole blood and you now want to collect 500 ml units of whole blood, this would be considered a major change in the solutions used to collect a blood product.

[Slide]

An example of processing changes would be new or revised recovery procedures. For leukoreduction it may be a new or improved process, a new generation of filters for red blood cells or platelets, or a new apheresis instrument.

For irradiation, products may be processed with new technology or it may be a new product being irradiated.

For freezing and deglycerolizing products, products other than red blood cells may be frozen using new instrumentation.

You may be rejuvenating new products with new solutions. These would all require prior approval.

[Slide]

Other processing changes that may apply to the blood and plasma industry would be a switch from manual to automated collection of platelets, fresh-frozen plasma, red blood cells, leukocytes, granulocytes plus future blood products.

Immunization programs for source plasma facilities, especially red blood cell immunization, would be

considered a major change.

Disease-state collection, such as autoimmune condition antibodies or high risk collection such as HIV antibody collections and hepatitis B surface antigen collections would also need prior approval.

[Slide]

The SOPs listed on the next two slides are critical procedures for both patient and donor safety. We want to review major changes for these important procedures. Please highlight the change or list the relevant pages in the cover letter.

If you are implementing a more stringent requirement than that recommended by us, such as adding a more stringent donor question, notification is not required. The SOPs that we do review are donor suitability, to include donor deferral; blood collection, to include arm preparation; high risk behavior question; AIDS information; donor history questions, to include informed consent. This is especially important in the plasma industry because your source plasma donor programs for red cell immunization and other immunized donor groups -- it is critical that these donors know the safety implications involved in the donations.

[Slide]

A final list of SOPs that we would consider major are, of course, your blood manufacturing process, quarantine and disposition of unsuitable product and, of course, any relevant future processing steps.

[Slide]

Prior approval labeling changes -- submit FDA form 2567, the transmittal of labels and circulars. Describe the product change. I have omitted one critical part of this, do submit the label and, you know, past it onto an 8.5 X 11 sheet of paper. This should be referenced. They are not really supplements but they do require prior approval before implementing the change. Again, it would be a new blood product, change in the standard amount of whole blood collected from 400 ml to 500 ml. Also, in the plasma industry, disease-associated antibody collection labels are also required and need prior approval before distributing the product. Other changes for the new amount of anticoagulant and other solutions will be covered in a lower category.

[Slide]

Finally, every important proposed change to a product or process that affects the safety and effectiveness of a product or process must be evaluated according to its risk. If the risk is substantial the supplement should have

prior approval. Before implementation of the major change, wait for approval from our director. Don't risk an interception or a fumble.

Thank you. Now I would like to introduce Patricia Gardner, who will discuss changes being effected in 30 days.

CBE30 Supplements - 21 CFR 601.12(c)

MS. GARDNER: You will probably find out why I became a med. tech. and not a mechanical engineer -- I will have these slides going back and forth. I am not very good at mechanical things.

[Slide]

I guess by now you feel pretty logged down, but wouldn't it be great to be logged down in the beautiful country of Finland!

[Laughter]

[Slide]

My topic is CBE30 supplements.

[Slide]

This is a cartoon of Herman, and poor Herman is sick, in bed. And his wife has just given him a great, bit tablespoon of medicine and Herman is having apoplexy because it tastes so terrible. So, his wife goes back and rereads the label and she says, "my mistake, Herman. I was supposed to rub it on your chest."

[Laughter]

Instructions can be so very important. So, it is my hope that by the end of my talk, as it is everyone's desire here today, our training will clear up any confusion so that you can apply all the new guidances correctly.

[Slide]

Under 601.12(c), changes to a product, production process, quality controls, equipment, facilities or responsible personnel that have a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of the product as they may relate to the safety or effectiveness of the product require submission of a supplement to the FDA at least 30 days prior to distribution of a product made using this change.

The requirements for the content of these supplements are the same as for those requiring approval prior to distribution. To reiterate, CBE30 stands for changes being effected in 30 days. The CBE30 category has the moderate potential to have an adverse effect on the product. I will be going through the guidance document that is listed in your workshop book under Tab 14 for changes later, and giving specific examples.

[Slide]

To clear up any misunderstanding that you may have

about the CBE30 supplement at the beginning, I am going to take the liberty of explaining what the CBE30 is not. These are supplements that will be reviewed and approved, but it is not a 30-day review and approval. FDA is not obligated to review and approve the supplement within 30 days. The firm can institute the changes in 30 days, but you must understand that you do it at your own risk. There may be occasions where FDA cannot approve your supplement and you may have to recall your product.

[Slide]

Now that I have discussed what the CBE30 is not, let's try to understand what it is. Why did FDA ever consider a category such as this one? The answer is that blood firms wanted greater autonomy over their businesses. Remember the old adage, "be careful what you ask for; you must might get it," and it isn't a Toyota. Firms wanted to be able to make changes without waiting for FDA's approval, hence, the category changes being effected in 30 days. If you submit under the change, please make sure you know that the submission was received at FDA. The firm is responsible for tracking the 30 days. I would recommend Fed. Ex. or U.S. Postal Service with return receipt requested so that you will know when the 30 days start.

[Slide]

Under CBE30, the firm must request this category with its submission. The final rule states that the supplement shall be labeled supplement changes being effected in 30 days. Blood and Plasma Branch will look over the submission to determine if the submission is complete and in the right category. FDA will notify you in writing. This notification has been incorporated into our current reference number assignment letters.

Some examples of these letters are as follows: We disagree with your assessment that this is a CBE30 supplement. The proposed changes, as described, do not meet the conditions described under 21 CFR 601.12.(c). This is considered to be a prior approval supplement and requires CBER approval prior to distribution of the product made using this change.

Or, you may get a letter stating that we received your CBE30 and that it is in the correct category but that it is not complete. The letter would list the deficiencies of the submission, and further state that the distribution of the product will not commence until FDA determines that all the information has been received. This information should come to us within 45 days or there may be sufficient grounds for refusal to file your application.

Another letter that you may get will state that

FDA recognizes that your submission is in the form of a CBE30 supplement and the continued use of the change is subject to final approval of the supplement. That is the one you want to get.

If there is a serious concern with the submission, the CSO makes sure to notify you initially by phone to discuss the deficiencies. The notice of the within-30 days will be the FDA date stamped on the letter that we send back to you. It is not the day that you receive it in the mail. FDA cannot be responsible for the delivery of the U.S. mail. That would be a responsibility too big for anybody.

Under CBE30, in 30 days you may effect the change. This means that you can distribute the product or transfer your testing to a contracted laboratory. So, you have decided that you are going to put these changes into effect in 30 days. Meanwhile, back at the Blood and Plasma Branch, the review will continue under the current managed review time frames. And that is all there is to the CBE30.

[Slide]

I am now going to go onto the guidance that is dated July, 1997, called changes to an approved application, biological products. As I mentioned before, this is under Tab 14 of your workshop. You must keep in mind that this document was written for the entire CBER -- therapeutics,

vaccines and blood. As it is written, it may seem confusing. So, Blood and Plasma has gone through it and made adjustments where we think it is appropriate, and we will try to put out a future guidance apropos blood.

You will find the CBE30 section under Roman numeral III, starting on page 5 of the guidance. The numbers on the following slides are the ones that the Blood and Plasma Branch felt pertained to our industry. The numbers on the slide are not consecutive but correspond to the numbers in the guidance document under CBE30. I put them on the slides for your convenience so you can go back later and read them for yourselves.

[Slide]

Number 1, automation of one or more process steps without change in process methodology. One example to be submitted under the CBE30 category is putting in an already functioning computer system in another facility. Of course, you will have to perform all the validation steps at the new place.

Number 5, the guidance uses the term responsible individuals. Remember, this guidance under discussion was written independently of the Federal Register notice for the responsible head so the terms don't match. However, the accurate term should be "authorized official," and they have

discussed this in previous talks.

Blood and Plasma has downgraded the change of "authorized officials" to a notification. Notification is not one of the new categories, but Blood and Plasma does not feel that FDA needs to approve your managerial personnel. But we also recognize that we need to know to whom to communicate. So, it isn't appropriate to downgrade it to an annual report. So, we decided to make it a stamp-acknowledged as long as you use the proper verbiage, "authorized official."

[Slide]

This slide will illustrate that the responsible heads are dead bit, never fear, they have been "touched by an angel" from the popular TV show --

[Laughter]

-- and have been transformed into the authorized official or AO. As discussed before, please notice the responsible head and the authorized official are not equivalent.

[Slide]

Modification of an approved manufacturing facility, that is, remodelling. The guidance talks about modification of an existing manufacturing facility. Modification to a vaccine or a therapeutic establishment

could be quite involved, such as changes in prep. rooms or filling operations where sterility is an issue. The CBE30 classification would be appropriate for them, but for blood facilities, such as donor centers, the moving of a donor bed from a south wall to a north wall isn't earthshaking. So, Blood and Plasma has downgraded this to be included in the annual report.

Number 8, change in donor testing. As discussed in the previous slide, after 30 days you may effect the change in your donor testing lab but Blood and Plasma will continue to perform a compliance check before approving a change in your donor screening testing. So, there is some risk if you choose to transfer your testing before the approval and the compliance check isn't okayed.

If you plan on effecting the change in 30 days for outside donor screening testing, stack the deck in your favor. When you first contemplate doing contracting of testing, if possible, visit the sites you have chosen as potential candidates. Look at their operations, their proficiency testing, the results of their FDA inspections and their previous 483s. See if they corrected the violations system-wide. Remember, you are responsible for the donor screening testing whether you perform it in-house or you contract it out.

Number 9, change in structure, name, location of legal entity that requires license reissuance. If you change the location of your licensed facility, please include the registration form.

[Slide]

Change in automated plasma collection for source plasma. This applies to existing approved automated plasma systems when you choose to change the manufacturer, for example, from Haemonetics PCS to Fenwal Autopheresis. This involves changing from one operating principle to another.

Also note that a change from manual to automation is a prior approval supplement, a PAS, while upgrades in machines, like Haemonetics PCS to PCS-2, are included in the annual report.

Number 14 involves changing your mailing address, moving your establishment or permanently closing your establishment. With all of these, please include a registration form.

While waiting for a new license, adding a new program or clearing up inspectional issues, source plasma places are allowed to collect product. Because of the lack of space on the premises, FDA has allowed source plasma places to ship the product under quarantine to an off-site storage place. These products may not be distributed

interstate, however.

[Slide]

In the guidance, under number 16 is a request for variance if FDA has published guidances, such as infrequent donor collection at the blood establishment and hepatitis under 11. When you read the guidance, the infrequent donor collection was listed separately under 17, but we have incorporated it under number 16 to be consistent.

You will notice that two of the samples in the middle of the slide have been crossed out. When we first put this seminar together we had put them under CBE30 but, with more brainstorming, we decided that they more readily belonged under the PAS category. You will need to correct your handouts, and I am sorry for any confusion this causes you. This ends the instruction of CBE30 supplement.

[Slide]

As Becky discussed, there is a subset of CBE30, called CBE, that is found in 21 CFR 601.12(c)(5). In certain circumstances, FDA may determine that based on experience with a particular type of change the supplement for such change is usually complete and provides the proper information. And, on a particular showing that the proposed change has been appropriately submitted, the product using the change may be distributed immediately upon receipt of

the supplement by FDA. The 30-day wait is waived and the product may be distributed after FDA receives the submission. This is still considered a supplement, however, and the firm must also request the CBE. The cover letter should contain the verbiage "supplement, changes being effected."

Some examples of the CBE category would be the use of SOPs that were previously approved for another firm. You decided you would use firm A's SOP and they said you could, so you send it in as yours. So, you could send this in as a CBE. However, you use the same SOP as approved with no changes.

Another category that could come under CBE is change in labels. These are minor changes in labels, and you use the uniform labeling guidelines. The other change could be that you change the additive or anticoagulant. You are already approved for red blood cells but you want to use another anticoagulant, or you want to use an additional additive. You may send in the label and start distributing the product.

[Slide]

Here we are, altogether, making beautiful music for the good of the nation's blood supply. Thank you for your time and attention.

DR. LEE: Thank you, Pat. I believe it is time for a break. I am told that the break at this point is half an hour long. I would like to remind you that there are evaluation forms in your folders, and please be sure to complete them and return them at the registration desk. The evaluation form is yellow, in the front folder of your packet.

[Brief recess]

DR. LEE: We are now down to our two final speakers before we hold our afternoon panel discussion. The first of the two remaining speakers is Miss Judy Ciaraldi, a reviewer with the Blood and Plasma Branch. She will discuss for us the specifics of the annual report as it applies to the blood and blood components industry. Thank you.

Annual Report - 21 CFR 601.12(d)

MS. CIARALDI: Before I get started, I wanted all of you to know how much work and time and effort it took for everybody to put this workshop together. I would like for us to have a round of applause for all the speakers so far.

[Applause]

Thank you very much, and don't forget to applaud after my talk too! I don't want to be left out!

[Laughter]

[Slide]

All my slides are in Tab 8. This first slide is just an outline to help you follow my talk. I am going to start with an introduction where I am going to define the regulation as it pertains to the annual report; spend a little time about the report date. We have already gotten some questions and I think I will address most of them during the course of my talk. I will go over the reporting procedures. Specifically, I will discuss the reporting format and the reporting period, what time frame should be included in your report. I will go over some examples of minor changes. These come out of the guidance document to some extent, in Tab 14. I will include what should and should not be on the annual report. I will briefly go over our review procedure at CBER, and I will finish with a summary.

[Slide]

Under the new requirements set forth in the final rule for 21 CFR 601.12(d), all applicants are now required to submit annual reports to FDA -- all applicants are now required to submit annual reports to FDA.

[Slide]

The minor changes in this category have a minimal potential to have an adverse effect on the identity, strength, quality, purity and potency of the product as they

may relate to the safety or effectiveness of the product.

[Slide]

The objective of my talk today will be to explain the reporting process. Specifically, I will discuss the reporting date. I will describe the reporting procedure. Again, I will list examples of minor changes that should be described in the annual report, and briefly describe our review process. It is my hope that after my talk you will be able to be more informed and less afraid of this new requirement. Any guarantees of that?

[Slide]

The annual report is to be submitted each year within 60 days of the anniversary date of the approval of the product application. I will say that again, the annual report is to be submitted each year within 60 days of the anniversary date of the product application approval.

What does within 60 days mean? It means plus or minus 60 days of the anniversary date. We will not consider your report delinquent until after the 60 days has elapsed. But, yes, you can submit it before that time.

[Slide]

Originally annual reports were to contain information about a specific product. A separate report was written for each product manufactured by a firm. As an

example, if a firm manufactured three products, then they would need to submit three annual reports on the anniversary dates of the approval of each product application. Of course, this is not practical for the blood and plasma industry because many blood and plasma firms hold more than one approved product application, often at more than one location. Well, we knew this and the regulation was revised to accommodate this practice.

[Slide]

On October 29, 1997, CBER sent a letter to all licensed blood and plasma establishments notifying them of the approval date of their first product application. If this date in the letter is acceptable to you as your annual report date, you do not need to notify CBER. If the date we stated in that letter of October 20 is okay with you, just hold onto it. You do not need to notify us.

[Slide]

The rule also states that a license holder or applicant may apply to CBER in writing for an alternate report date. You may select this date to coincide with a convenient reporting period or a date for your corporation. You can pick it for any date. You can pick it to match your birthday if you want. It is your decision on that. Once this date has been approved by CBER, the annual report must

be submitted within 60 days of this alternate date.

[Slide]

The October 20 letter only listed the approval date for the first product application. We assume that blood and plasma establishments will want to report changes for all of their different products at one time. In other words, we assume that you would like to bundle all the minor changes to all your products into one annual report. The rule states that all minor changes to any and all approved product applications held by the firm may be reported in one annual report. This also includes changes that took place at any and all locations operating under the control of the applicant or license holder or under contract to the applicant. If this is acceptable to you, you do not need to notify CBER. As Dr. Devine has said, we think that this would probably be the best option for you, but you do have the option of separating them out if you want to.

[Slide]

There are three main sections we expect to see in the annual report. First, we expect to see some sort of cover sheet or cover letter. When the BLA becomes effective next year for blood and plasma, the BLA cover sheet, the 356h, should be used and you should mark the annual report box on the front page.

Until the BLA becomes effective for blood and plasma just use your own cover sheet as the first page of your annual report. Now, what to put in the cover letter? Include a brief summary of all minor changes made to the approved applications that affect safety and effectiveness of the product. This brief summary can be in the form of an outline or a bulleted list. It doesn't have to be in any great detail in the cover letter.

Follow the cover letter with a full description of minor changes reported to the approved applications. You would include in this full description a list of products affected by each change. Describe that the change took place at all locations, or add an individual or specific location. If it did not take place at all locations and you are informing us at which locations your change took place, you should include the registration number and the address of those locations. Include the date the change became effective or was implemented.

As you have heard before, you may cross-reference relevant approved SOPs or approved prior comparability protocols. If you are referencing prior approvals, it would be helpful to include the reference number of BLA number for these approvals so we know exactly what you are referring to.

[Slide]

I would like to remind all of you, as all the speakers have, to be as detailed as necessary in order for us to fully understand the change. Even Moses needed a little more information!

[Slide]

A more specific reporting format will be described in the guidance document that we are developing for the blood and plasma industry on the reporting of changes. I stress that it will be a reporting format that we will be helping you with.

[Slide]

The reporting period covered by the report should be included in the cover letter or on the cover sheet, the 356h form when it starts to be used. The reporting period should cover 12 months of operation, and it should be timely and current to the report date. We recommend that the reporting period close no more than 60 days before the report date. We want the information on it to be as current as possible.

[Slide]

The reporting period for the first annual report may need further explanation. Now I am going to have you guys do a little bit of work here. I am going to have you

add two sets of numbers. Behind October 7 add 1997 and behind January 20 add 1998. If your anniversary date that was presented to you in the October 20 letter is between October 7, 1997 and January 20, 1998, you will submit your first report in October, '98 to January '99 within 60 days of the applicable anniversary date. You will include the changes implemented since the rule became effective, since October 7, 1997.

I have an example to illustrate this. For instance, if your anniversary date falls in December, 1998 you would file your first report within 60 days of the December, 1998 anniversary date. You would include information on changes implemented from October 7, 1997 and thereafter.

[Slide]

This first annual report will contain more than 12 months in its reporting period, but that is only for the first one. After that we just expect to see 12 months of information.

If your anniversary date is on or after January 20, 1998 file your first report within 60 days of the applicable anniversary date in 1998. Include changes implemented since October 7, 1997. As an example, if your anniversary date falls in July, 1998 file your first report

within 60 days of the anniversary date in July, 1998. Include information on changes implemented from October 7, 1997 and thereafter.

The reporting period for these first annual reports will be less than 12 months but, again, this is only for the first annual report. After that the reporting period should cover 12 months.

[Slide]

Submit one original annual report and two copies to CBER.

[Slide]

As a review, when referencing a change implemented using an approved comparability protocol, this is one where a change has awarded you the privilege to downgrade your report of that change to an annual report. Include the reference or BLA number for the supplement approval.

When referencing the SOPs, include the title and procedure number, as well as the implementation date for the procedure. You are giving us the type of detailed information we need to make sure we understand your annual report. The specific examples I am going to start citing are not all-inclusive. They are only meant to help you decide what kinds of changes belong on the annual report.

[Slide]

First, a change in shipping conditions based on data derived from studies following a protocol in the approved license application. This may not fit into the blood and plasma industry a whole lot but I have thought of one example. My co-workers helped me think of one example where this would apply. Changing the shipping conditions for either a product or a sample from that that was originally stated in a contractual agreement that was part of an approved application. So, there is an approved SOP. There is an approved contractual agreement that states how the product should be handled and shipped back and forth as part of the application, the original application. If there is a change in that, and it is based on successful data that the product will not be compromised, then you can report that in the annual report.

Also, a change or addition of equipment with that of a similar design and operating principle. A couple of examples of this are changing from a Nordion to a CIS irradiator or upgrading from a Haemonetics PCS to a Haemonetics PCS-2. All this equipment must be 510(k) cleared.

[Slide]

Also include organizational changes that have occurred since the last report, and include the current

organizational chart with descriptive job titles and names. As Gil mentioned, you do not need to double report. If your most current and up to date organizational chart was submitted as part of a supplement, then you do not need to include it again if there are no changes. But if there are changes that have been made, then you can just note them on the annual report.

Facility changes which have occurred since the last report should be also included in your annual report. When there is a facility change send in a registration form, 2830, within 5 days of the opening of the facility.

[Slide]

Some examples of facility changes are on this slide. First, the addition of a distribution center. Next, the move of a donor center, including centers at which blood components are prepared. If there is a move within the same building and there is no address change, you do not need to send in a registration form. Third, addition of a new fixed blood collection site at which only donor suitability determination and whole blood collection is performed.

As an aside, just as a reminder, if there are permanent closures of a facility or a donor center, CBER should be notified as soon as it becomes effective. You can do this by sending in a registration form with a cover

letter stating that the facility has been closed, and we will process this under a CBE30, as Pat had mentioned.

Last type of facility changes could be room upgrades, remodelling and alterations. An example would be improving your donor screening area for more privacy. That would be something that would be nice to know.

A change in contractual agreements -- now, these are only changes in those contractors that are not part of an approved product application. Gil went through all the types of contractors that should be part of applications or supplements. He listed some of those that do not need to be included. If you have a change in that list of the types of contractors that do not need to be included, then a change in those types of contractual agreements can be put in the annual report.

An example would be a change in the test lab that performs confirmation testing or performs your QC testing. This can go in the annual report. If you are using the test lab to perform biomarker testing for donor reentry, then that should go into CBE30. Include also a change in doing business as name that does not affect the license establishment name, in other words, one where we would not have to reissue a new license.

[Slide]

A change in blood establishment computer software vendors or a version. If you are currently using, for instance, a Serner information system for electronic cross-match and you are converging to a Metaware information system also for electronic cross-match, you can cite this on the annual report. A change in license test kit manufacturer, changing from Ortho to Abbott reagents.

[Slide]

Implementation of automated equipment or ABO/RH syphilis and viral market testing would be described in the annual report. The equipment, again, must be 510(k) cleared, and the equipment should be used according to manufacturer's instructions.

Include if you have started collecting source plasma from donors with preexisting disease-associated red blood cell and/or HLA antibodies. Of course, you need to be previously licensed to collect source plasma in order to add this into your program.

As Joanne mentioned, the labels have to be previously submitted, reviewed and approved before they can be used.

As an aside, if you intend to collect source plasma from these types of donors, we recommend that you follow the procedural items addressed in the draft

reviewer's guide, disease-associated antibody collection program. This document was made available on the CBER fax document system in October of 1995, and it is very useful because it lists the preexisting antibodies that are allowed to be collected and reported in this manner.

[Slide]

If you implement an FDA approved uniform procedure, a uniform donor history form or circular of information, you can put that on the annual report. Since these uniform procedures do get revised from time to time, please include which version you are using. If the applicant varies from the uniform procedure for their own use, they must submit a prior approval supplement with the rationale and data to support the use of the alternative procedure. If you have substituted the uniform procedure, one of your own questions, it is no longer the FDA approved uniform procedure and it becomes your own procedure and we must approve it first. An exception to this is if you implement a stricter or additional requirements, like asking a donor about exposure to tick-borne disease, then no prior approval is necessary. Just state that you have done this in your annual report.

[Slide]

Implementation of FDA recommendations that are

contained in guidance to blood establishments, they can be reported on the annual report. Again, if you vary from the guidance document you must submit a supplement under the prior approval supplement category, and include the rationale and data to support the alternative procedure. An exception to this would be if the memo or guidance refers to a variance to the regulation, this may require a prior approval or changes being effected submission supplement. Be sure to read the guidance document and its requirements very carefully. It will be stated what needs to be done.

[Slide]

There is a smaller list of items that are not included on the annual report. These are changes reported in previous annual reports if there are no changes. You don't need to tell us again the things that you have told us before if there are no changes.

Changes that received approval as supplements during the previous year. Remember, if you submitted them as a PAS or CBE30, those described major or moderate changes and do not belong on the annual report. The annual report contains only minor changes.

Also, do not report changes submitted as supplements and currently under review by CBER. Again, those supplements are major or moderate changes. In other

words, there is no need for double reporting.

[Slide]

Also, do not include informing us of the shipment of inadvertently collective, repeatedly reactive units. The CFR states that these must be reported either each time the shipment is made or twice a year, in April of October. A revision of this reg. is being considered and it is hoped that in the future these shipments may be put on the annual report, but for right now follow the regulation. Right now do as you have always done.

You do not need to include the development of unexpected antibodies in donors who participate in red blood cell immunization programs. This is a revision from what is in the July, 1997 guidance document and it will be included in the new guidance document that we are developing. The unexpected antibodies from these types of donors still need to be kept on file for review during inspections. When I say this, I am not saying it to make you think that we are not concerned about the practice of the red cell immunization program. In fact, CBER has a renewed concern of the practices in these programs, including the development of unexpected antibodies. But this is not really a change in manufacturing and, therefore, does not belong on the annual report.

Lastly, do not include error and accident or incident reports and recalls. These should still be reported in the same manner as you have always done in the past.

[Slide]

The annual report is not a supplement. We will not approve the changes in the annual report. We know that when you first heard about the annual report requirement you had maybe a few concerns -- is that an understatement? The first was whether or not the report would be reviewed by CBER. The answer to this is yes. The annual report will be reviewed by CBER for correctness of the categorization of the changes included in the report. In other words, we are going to ask do these changes belong on the annual report.

[Slide]

Another concern was whether CBER will communicate with you about the annual report. The answer to this is also yes. "Yes, sir, I went through your report just a moment ago," and t here is the report.

[Laughter]

Because my bosses are here, I have to guarantee you that my golf handicap will not improve after reviewing annual reports!

[Slide]

We know that there is going to be a learning curve about annual reports. If the annual reports contain some changes that should have been submitted as supplements, CBER will communicate with the applicant and inform them to submit the change as a prior approval or a CBE30 supplement as soon as possible.

We will also communicate with the applicant if the report is delinquent. And, brand-new that is not on my slide, it was just decided that we will acknowledge the receipt of the annual report. The actual mechanism by which it will be done is still being finalized in its detail. We will not acknowledge that the review is complete, at this point, unless there are problems. We will acknowledge that we have received it. After the review the report will be placed in your license file.

[Slide]

Now to summarize what I have presented, all manufacturers holding approved product applications must now submit an annual report to FDA describing the minor changes in product, production processes, quality control, equipment and facilities.

The annual report is to be submitted within 60 days of the anniversary date of the first approved product application. The applicant may request an alternate date

that must be approved by CBER. If the product approval date, described in our October 20 letter, is acceptable to you, no notification to CBER is required.

[Slide]

The annual report should describe minor changes that have occurred since the reporting period covered in the previous annual report. In other words, include only new information.

The annual report may include minor changes for all approved product applications occurring at all facilities operating under the license holder. In other words, you can bundle it together in one annual report. The annual report should include those types of changes or information that I described in my talk.

[Slide]

The blood and plasma establishments will submit their annual reports to the Division of Blood Applications in the Office of Blood, Center for Biologics. If there are no changes to the product applications that have occurred since the last annual report, while it is not required, we recommend that you send in a cover letter stating this so that we know that you are not delinquent in submitting an annual report.

Remember, Dr. Devine stated that there are some

strict penalties for failure to comply with this new regulation. One of them is that all of your changes might need to be reported as a prior approval supplement. That means changes that I just described to you that would go in an annual report would need prior approval before you can distribute. Now, there is only one way we can track that you are not delinquent and that is for you to just drop us a line and say there have been no changes.

[Slide]

As you get ready to submit your annual reports, you may call us with questions. The Division of Blood Applications phone number is (301) 827-3543. Or, you can fax us a question at (301) 827-3534.

[Slide]

Or, you can write DBA at 1401 Rockville Pike, Suite 400 N., Rockville, Maryland 20852.

Thank you very much for your attention.

[Applause]

I trained you guys well. Thank you. I would like to introduce my boss, Mary Gustafson, who will now talk about the comparability protocol. Thank you.

Comparability Protocols

[Slide]

MS. GUSTAFSON: First of all, we have to learn how

to pronounce comparability protocol or comparability protocol. I actually looked it up in the dictionary, and it has been a long time since I took grammar so I had neither the time nor the patience to sort through all of those little squiggles, those upside down "e's" and parentheses, slashes and all of that. But I kind of think it is like one of those words like tomato and tomato. So, anything goes.

[Slide]

First of all, the concept of a comparability protocol was not addressed in the January 29, 1996 proposed rule for changes to be reported to an approved application. This concept of a comparability protocol was developed in response to the comments to the proposed rule, requesting that more categories of changes be placed in lower reporting categories. In response to these comments, a section was added in the final rule at 21 CFR 601.12(e) that describes use of a protocol in reporting a change in manufacturing.

Basically, a comparability protocol is a protocol that describes how a change will be managed that is developed and provided to FDA prior to implementation of the change. The idea is that if an applicant can demonstrate to FDA how it will manage the change, FDA will be more comfortable that the change can be effected without causing harm to the product, and will allow reporting of the actual

change under a less burdensome reporting category.

[Slide]

The protocol described in 21 CFR 601.12(e) is requested as a prior approval supplement. The protocol describes a plan for implementing change and includes testing, and validation studies that will be performed in evaluating the change and its effect on the product. It also defines the criteria and acceptable limits against which the impact of the change will be evaluated.

After approval, the change can be implemented using the protocol with a lesser reporting category. In most cases, this would move a change from a prior approval supplement to a changes being effected in 30 days supplement. However, there may be instances where greater reduction in reporting could occur.

[Slide]

The comparability protocol assumes that industry operates under protocols developed to analyze and facilitate change. This is important because this is what the biological drug manufacturers told us. Protocols for change are already developed and utilized by firms to plan manufacturing changes. Submitting this already developed, routinely prepared plan to FDA affords industry the option of allowing FDA review and approval of the protocol and, if

approved, the change can be facilitated with less burdensome reporting.

[Slide]

This is basically a tradeoff. Industry allows FDA to evaluate the applicant's ability to effect change. By doing so, FDA has greater assurance that the change is being properly evaluated, and that there is less potential then for the change to have an adverse effect on the product. Therefore, FDA will be more comfortable with a lower reporting category of the actual change.

[Slide]

It is important to note that use of a comparability protocol approved by FDA might not justify a reduction of the reporting category for every type of change. Some steps in manufacturing are so critical that a change would always be subject to a prior approval supplement. I have heard colleagues and other offices tell me that they are already receiving ideas from manufacturers that they would like to use the comparability protocol to build entirely new facilities, that would scale up manufacturing by 50 times. So, there are some changes that are so major or so critical that we probably still would require a prior approval supplement even if we approve your protocol or look at your protocol.

[Slide]

Because the notion of the comparability protocol was not in the proposed rule and we did not receive industry comment on it because it became part of the final rule, we requested industry input on use of comparability protocols at an open public meeting on September 24, 1997. The biologics industry, including the Coalition for Regulatory Reform, provided comment.

Because the comparability protocol was a new provision in the final rule, that is, it was not conceived in the proposed rule, and because the description in the final rule is broad and general, the comments received were as varied as the audience. It seemed that everyone had a little different spin on what they perceived a comparability protocol would be and how it could be used.

One unified message, however, was that the comparability protocol is not a one-size fits-all plan that easily translates from one applicant to the next or one manufacturing process to the next. The content of a protocol may change depending on the type of change being effected, and depending on the applicant and the manufacturing arrangements utilized by the applicant.

[Slide]

In distilling comments and looking at our work

in-boxes, I have listed some possible changes that may be amenable to submission of a comparability protocol. These include implementation of a change in multiple facilities. This could be upgrading equipment and/or methods used in component manufacturing.

Another candidate for a comparability protocol might be the acquisition of facilities operating under one license by another licensee. This is typically what is called a rollover in the plasma industry. Currently, in a rollover one licensee acquires the manufacturing facility equipment and assets that are operating under another license number.

Our processing and the industry's cooperation in this effort contains elements of artificiality. We rollover the location license based on the assumption that there are no operational changes when, in fact, the new owner wants, desires and needs to assimilate that facility under its manufacturing methods and controls. So, we see a lot of changes either right before the acquisition or changes right after the acquisition. So, why couldn't we work with the manufacturer ahead of time and, in the context of a comparability protocol, see what his plan is to acquire the facility and bring it under his own manufacturing umbrella?

It could also be used, I think, when there is a

single change with a long planning stage and a short implementation timetable. I don't have any real specifics but I would think that a situation whereby a single manufacturer has test laboratories at multiple facilities and decides, for efficiency, that he wants to consolidate the testing in a centralized facility that will be larger and perhaps have -- well, obviously have added equipment. I think we would foresee reviewing the change plan ahead of time because in most instances, and we know this, the manufacturer has a really short timetable to implement the change then because, you know, people get real antsy when they know their jobs are going to be eliminated, and it is kind of human nature that they go out and look for new jobs. So, if there is not a way that they can fairly quickly switch from multiple facility testing to the centralized testing, there is really a problem in staffing those multiple sites. So, I could foresee that this would be a situation where we could work with the manufacturer under a comparability protocol to effect the change.

[Slide]

These are only a few of the possible uses of a comparability protocol. Your input to develop this list is welcome. Also welcome is your input into possible elements of a comparability protocol. Here are some areas that we

see as appropriate for a protocol review. These are possible elements of a comparability protocol. They may not be appropriate for all changes, and there may be additional elements for other changes.

First of all, we need to see a description of the change with relevant SOPs; the validation protocols that would be used to validate the change, including the tests that would be performed and the expected results; a training protocol if the change involves training new or existing staff in a new method; what your quality assurance plan is for oversight during the change process; and your implementation or roll-out plan if the change affects multiple facilities operating under one license; also, there may be some times where labels would be relevant as part of this comparability protocol.

[Slide]

The comparability protocol is an option under the regulations. It is not a mandate. In many cases submission of a comparability protocol may not be worth the additional up-front effort in preparing and submitting the protocol. It may be just as easy to submit your change and have it reviewed as a prior approval supplement. So, it is an option. It is not something that you even have to consider, although I can see that it will be useful for blood and

plasma manufacturers.

It appears that the comparability protocol is situation specific rather than generic. Although it was clear in our September 24 meeting that trade organizations present had attempted to develop templates to genericize the protocol, the general conclusion is that any protocol is specific to the situation. We would caution that there does not appear to be a cookie-cutter template that, if followed, will fit all situations.

Additionally, the comparability protocol may be a useful planning tool. This is a reality even if you decide it is not worth the effort of having it reviewed an approved. Operating under a system that actively and formally plans for change can only be a benefit to your organization.

This concludes our formal presentations for today. I will now invite the panel members to come on stage and I will turn the program over to our moderator, Dr. John Lee. Thank you, all.

[Applause]

Questions and Answer Period

DR. LEE: Thank you. While we are relocating, I would like to take this opportunity, just in case I forget to do so or we run out of time at the end, to recognize that

this workshop has been made possible by a contribution of a number of people. I would like to thank all the members of the Blood and Plasma Branch particularly for making this happen in this way. Also, I would like to particularly thank the following members of the Licensing Workshop Planning Committee: Janet Ishimoto, would you stand up please and be recognized.

[Applause]

Jane is a reviewer within the Blood and Plasma Branch and she has been instrumental in organizing this workshop. Along with Janet, Joe Wilczek -- would you please stand and be recognized?

[Applause]

Thank you, Joe. And, needless to say, Judy Ciaraldi, Ken Zeeman and Gil Conley have been also participating in the coordination of this workshop, as well as being presenters. Mr. Zeeman has not presented today but he has also been instrumental. Mr. Zeeman?

[Applause]

I guess I have to fire away the questions now. I think using this 3 X 5 card method is a mistake. There are too many questions here!

[Laughter]

I think we will try to get through as many as we

can and do what we can. However, in glancing through them, I recognize that many of these questions were submitted prior to the appropriate presentations, and sometimes the questions are also duplicative of each other. I don't know whether that is because of timing issues or what, but I think I will sort of cull through them and I may not specifically answer every one. If you still feel that your concerns are not answered by the time this panel discussion is over, or close to being over, please step up to the microphone and discuss questions more specifically.

I will start with a question directed at Ms. Denham. Ms. Denham joined us as a panel member here. She is also a reviewer in the Blood and Plasma Branch. The question reads, will a transition notification letter be sent to the applicant even if CBER agrees with the chosen category? Will it be sent to the applicant within 30 days?

MS. DENHAM: It will be on your reference assignment letter, and it will indicate that we have accepted the category you have placed it in. I guess that will be in the 30 days too.

DR. LEE: There is a second part to this question. Do manufacturers need to call FDA for receipt of CBE supplement to determine when day 30 is official?

MS. DENHAM: That is your responsibility.

DR. LEE: Well, the 30-day I believe will start with the receipt date.

MS. DENHAM: That is why Pat suggested that you use some method where you can get a return receipt so you would know what day we received it.

DR. LEE: The next question appears to be directed to Miss Gustafson. Will there be a guidance document for the development of a comparability protocol? I believe you just addressed that. Yes.

The next question is also directed to Mary. What happens to the individual license number suffix? Do we continue to identify the facilities by this number under the BLA for many facilities under the license?

MS. GUSTAFSON: The location suffix to the license number was not an official number anyway. It was a number that was given for tracking purposes. In the future, with the BLA, since we will no longer have specific location licensing, we will use the registration number for tracking facilities under your license.

DR. LEE: Do all PASs require a PLA until BLA is in effect?

MS. GUSTAFSON: The answer is yes.

DR. LEE: Here is a question for Dr. Devine. Could you identify the difference between the annual summary

and the annual report? Is the annual report to be sent to the FDA directly or held at our facility until time of inspection? Well, the annual report should be sent.

DR. DEVINE: I am not sure I know what an annual summary is. If somebody is thinking of something they would like to clarify -- we talked about maybe somebody thinking about audits, their annual audits that they might do under QA programs. Those are not the same as the annual report. The annual report specifically addresses manufacturing changes, not your normal ongoing quality auditing, and such. So, the annual report really would include the changes only to manufacturing. So, it is submitted to us, and we have heard quite a bit about that in the talk so maybe that question was kind of coming before that.

DR. LEE: Thank you. The next question -- let me read it first; I can't figure out who it should go to. If separate licenses already exist for several establishments, i.e., manufacturing, donor centers, testing laboratories and several products, i.e., fractionated plasma derivatives as well as source plasma, how should changes to these individual licenses be handled in the future under the new BLA system? I think we talked about this essentially in the morning session.

MS. GUSTAFSON: The scope of this workshop is for

blood and blood components only. In terms of collapsing several product license applications into a single BLA, it is applicable to those products that are traditionally known as blood components. If you are a manufacturer who is licensed, say, for source plasma, which is a blood component and could be grouped with the other components, and also albumin and Factor VIII concentrate, you would be required to submit a separate BLA for those fractionated products individually. it is only the blood and blood components that are being collapsed into a single BLA. Otherwise, the transition to the BLA will affect your current BLA for that product and your establishment license application.

DR. LEE: The next question is directed to Betsy Poindexter. It reads, I thought a BLA supplement could cover a given product at all sites but not for apheresis. Is each site a separate supplement?

MS. POINDEXTER: With the new BLA form you can put as many or as few sites on one particular supplement as you would like. A lot of it will depend on how rapidly you think each of those individual donor centers can submit the quality control and the required samples to the Center to be cleared. We haven't addressed yet whether we could approve partial submissions and the rest would be held under another supplement number, amendment number. So, I probably

misspoke this morning in saying each facility needed separate BLAs. What they need are separate submissions for quality control and product submissions, but those can all come in on the same BLA if that is how you choose to submit them to the Center.

MS. GUSTAFSON: I did mention this morning that we are working with our computer contractor in terms of having some way to approve parts of a supplement. What we will probably do is spin off into another supplement number parts of a submitted supplement that is holding up other parts because we know that this will happen. We ask you not to bundle things excessively so that it is a routine practice, but yet we know that there will be times when, due maybe to a compliance problem in a facility or maybe due to inadequate manufacturing controls at one facility, that it is not going to be ready at the time that the other facilities are. So, we are going to try to simplify that for you, and it will probably be what we will call a spin-off supplement so that we won't hold everything up just for one outlier.

DR. LEE: Thank you. The next question is directed to Miss Ciaraldi. If FDA circular of information is modified to make it more stringent, as adding the phrase exposure to a tick-borne disease, does this information need

to be also included in the annual report?

MS. CIARALDI: The answer to that is yes. We do want to know what your processes are. You don't need to submit a prior approval supplement if you are taking the FDA uniform processes and you are not changing any of it as it stands, in other words, you are not substituting a question for another. But if you are adding a question to make it more strict, you can put that on the annual report, just stating that you have added this question.

DR. LEE: Thank you. Here is a question for Mary. Doesn't the comparability protocol require prior notice and comment for rule-making? It constitutes a significant regulatory requirement introduced only in the final rule.

MS. GUSTAFSON: The concept of the comparability protocol is in response to comments received and, according to the review of our counsel, was well within the scope of responding to comments within a rule-making. So, it is our feeling that it was well within the APA procedures to include that in the final rule.

DR. LEE: Thank you. This one is for Mary. If an applicant is not a manufacturer, what information needs to be submitted to demonstrate that the applicant can take responsibility for the requirements in Part 600 through 680?

MS. GUSTAFSON: Basically, everything. If you are

contracting, then it is your application; you are the applicant and you would submit all of the information to show safety and effectiveness of the product, including information that we would need from the contractor. That is one reason that we are keeping open the option of shared manufacturing and divided manufacturing because these arrangements are more attractive at times when manufacturers want to be responsible for particular proportions of manufacturing, but they don't necessarily want to share all of their secrets with the other manufacturer.

So, we are having a very flexible regulatory scheme. There can be contracting in which the applicant will be responsible for submitting all of the information, being aware of and responsible for all of those manufacturing steps at the contractor. There is also the option still of shared and divided manufacturing where those responsibilities are shared under the licensing process and they have separate application filings.

DR. LEE: Here is a question about the comparability protocol. How long will CBER have to review and comment on a comparability protocol, and in CBER's response to the comparability protocol will CBER define the reporting category for the change?

MS. GUSTAFSON: Currently, we will consider those

to be prior approval supplements and will review them under our current managed review time frames which, depending on the change, is either on a 12-month or 6-month scale right now. I will tell you that at the September 24 open public meeting that discussed the 601.12 changes there were numerous comments from the other parts of the biologics industry, not the blood and components side, that they would like a shorter time period for review of this comparability protocol. I don't want to put Becky on the spot, but maybe you have more information?

DR. DEVINE: For user-fee products the time frames for review will be heading downwards for prior approval supplements. Those will be going down eventually to 4 months. For changes being effected supplements, those will remain, for manufacturing supplements, at the 6-month time frame. In terms of the non-PDUFA products, we have been trying very hard to meet the PDUFA time frames, but as our resources continue to go down, down, down, I am not sure that we will be able to make the commitments to the 4 months on the non-PDUFA products. So, I would anticipate that those would remain at the current levels for manufacturing supplements that are prior approval.

DR. LEE: There seem to be a lot of concerns about the comparability protocol. This one ties rollover into

this area. The question reads, is a rollover of a plasma center still possible today, or must it be under a comparability protocol?

MS. GUSTAFSON: As long as we still have the ELA and the ELA filings, you can use the traditional rollover. But I would ask you to start thinking when we transition to the BLA and no longer have the discrete location licensing, you know, if you would find use of a comparability protocol a useful tool.

DR. LEE: Let me just add. This was pointed out in Mary['s talk but the question reads, is a comparability protocol required only once, or is it required for each change? Well, it is required once for the scope of the protocol, and then any change on that protocol would not have to be individually reported or reported as outlined in the comparability protocol. Does that need any further clarification?

DR. DEVINE: The regulation says that the protocol will cover specific changes, or specified changes. So whatever the scope of the comparability protocol is would be what would be covered. Then after you make the change you still have to report according to the category that was designated in the approval. So, for example, if it went from a prior approval supplement to a changes being effected

supplement you would submit your supplement 30 days before the change or if it was at the time it was being effected, if that was the agreement in the approval letter, then that would be what you would do. So, you may be submitting more than one comparability protocol for different types of specified changes.

DR. LEE: This one might be for Judy. Does moving a donor center, such as source plasma collection, only require annual reporting? I think this is different from moving a simple donor center for transfusion collection.

MS. CIARALDI: Yes, the donor centers, to my knowledge -- Mary will probably have to fill in some of this -- the donor centers are the ones that collect whole blood products. It is my understanding that normally the source plasma collection facilities are not called donor centers. So, I don't think that they are included in an annual reporting level. The location of a plasma center would be at a higher reporting level. Can you help me with that, Mary?

MS. GUSTAFSON: You stated that correctly, you know, as long as we still have the location licensing. I think as we develop the guidance document specific for blood and components, we need to take into consideration the transition to the BLA.

The guidance document that was published with the final rule for 601.12 actually started in development several years ago, long before we foresaw the notion of dropping the establishment licensing and going to a single biologic license application. So, as we develop the guidance, I think we will need to clarify some of these points as they relate to facilities operating under a BLA. It is a good question.

DR. LEE: The next question -- well, I will just read this out and anybody can jump in here. What if a new site is added which collects both whole blood and pheresis components, what type of notification is required? What if the pheresis components are not licensed? I presume this refers to which reporting category.

MS. GUSTAFSON: It would become a PAS at the time you want your apheresis products to be shipped under license. If you wanted under license only the whole blood that is collected there and then sent to mother house for processing, you would need to file a registration form within 5 days and then the facility would be reported on the annual report.

DR. LEE: I will just picked out a platelet question here because that end of the table is too quiet. This one is directed to Betsy. Is it permissible to

distribute platelets pheresis products with the license number obliterated while your institution collects data and performs validation before FDA notification?

MS. POINDEXTER: I guess it depends on what you mean by distribute. If you mean within your state, as long as you are collecting the product according to the manufacturer's instructions you can distribute it within your state without the license number. You cannot distribute it outside of the state.

DR. LEE: Here appears to be an interesting question. What are the consequences to an applicant who puts a change on the annual report and the FDA decides to change the category 6 months after the change was effected?

DR. DEVINE: I am assuming what you mean by that is that we go out on an inspection, or else we get the report and we find out you have made a change that should have been submitted in a higher reporting category, not a lower reporting category. First of all, if it comes in on the annual report, we will either notify you by phone or in writing that you need to submit a supplement. Then the status of the product may be dependent upon what the change was and what the potential effect might be.

If it was supposed to be a CBE30, then obviously distribution would not be a big issue. If it was something

that should have been a prior approval supplement and upon review we find that the appropriate validation and information was not collected, or that there was some adverse effect on the product, then it would depend on the severity of that situation what would happen.

In general, what we will try to do is if a company gets it wrong, we will work with them to try to have minimal disruption of product supply while we obtain the information that is necessary to get the supplement on file and approved. So, in general, you know, we don't really anticipate that this is going to be a problem that is going to happen very often. We know that with t he 30-day CBE and the annual report there might be some risk so companies will have to make decisions whether or not they want to withhold distribution themselves, or wait until they get some kind of a sign on what the review outcome might be but, certainly, they don't have to and are not obligated to wait.

The new law, by the way, has a provision in it which would allow us, if we do not approve the supplement, say, it was a CBE30 or something that should have been reported and we are not going to approve it, it does provide a provision for us to order cease distribution. So, that has been added to the new law, and it is not really addressed in our regulation but was addressed in the

preamble where we said we would try to work companies to achieve minimal disruption and cost to the firm, to try to make the problem be fixed.

DR. LEE: There is a short series of questions regarding annual report with respect to inspections. Will the information in the annual report be provided to the field investigators? How will reporting changes in an annual report impact on inspections, and have investigators been given any guidance on how to inspect AR changes?

MS. GUSTAFSON: We do plan on sharing the information in the annual report with the field investigators. We have not worked out the way in which we will do that. That is on the radar screen to be done in working with our Office of Compliance. That is one reason why we are asking for an original and two copies. However, for some multi-facility firms operating in many, many districts that still won't be enough. So, we may have to have some very novel ways of working perhaps through our biologics experts in terms of having the annual reports available for inspection.

We do imagine that there will be changes that investigators will want to look at in more detail in terms of determining whether you followed appropriate validation procedures and controlled the change process. We have not

issued any guidance to date to the field investigators. However, they are familiar with annual reports in the drug industry because they have been required for new drug applications for many, many years.

DR. LEE: The speaker on the annual reports said that all applicants must submit an annual report. Must an applicant submit an annual report even if it made no changes during the reporting year that are of the type that would be reported in an annual report?

MS. CIARALDI: It is not part of the rule but we recommend that you just send in a cover letter stating that there have been no changes. Again, one of the penalties that follow under the failure to comply is to not follow the rule, in other words, not submit an annual report. We don't know if you don't send us anything if you are delinquent in sending us an annual report and you do have changes, or there really were no changes. The best way to let us know that is to communicate with us, just in a cover letter, saying that during this reporting period you have had no changes that belong on the annual report. Then we will know you are not delinquent and we won't start putting you in the category where we need to watch you if there are repeated failures to comply with 601.12.

DR. LEE: That point was made clear in your talk,

yet, the question asked for it again. So, I guess there are still some doubts about the clarity. So, we will handle these questions as they come.

The next question is directed to Dr. Devine. Dr. Devine mentioned that guidance documents are not binding upon industry. Would you please discuss instances when the guidance documents are not binding for FDA, i.e., does not operate to bind FDA?

DR. DEVINE: If I said that, I misspoke. What I should say is that they are non-binding, and I think that is what my slide said. They are non-binding on industry and they are non-binding on FDA. However, FDA has made a managerial commitment under the good guidance practices that it will not deviate from its own guidances unless a reviewer obtains supervisory concurrence. That was a managerial decision that was made because one of the complaints we heard was that reviewers were applying more stringent requests than what would appear in guidance documents.

Guidance documents are non-binding for both us and you. So, again, there is always the opportunity for an alternative to be requested and approved by us under that system. So, I would encourage you, if you haven't looked at them, to review our good guidance practices document. It appeared in the Federal Register in March of this year. It

is on the FDA web site. The new law and the FDA Modernization Act has a section on policy-making and guidance which directs us to codify our practices. So, what you will probably see in the future is that the good guidance practices document will go through a rule-making process and will become codified. So, I think it is important for you to understand the process and what opportunities it avails you, as well as how we are going to be practicing.

DR. LEE: Thank you. Here is a question directed to Pat. Could you clarify the apparent discrepancy in Joanne's and Pat's talks. One stated change in solutions require prior approval. The other stated prior approval is not needed.

MS. GARDNER: Joanne's slide, slide number 8, states change in a solution in blood product collected. As Joanne and I went over the slide, she did mention that additives were the exception to this. What was included under this statement on her slide was if you change from 450 ml bags to 500 ml bags, that would be a prior approval. However, the additives were under the CBE, and you just have to submit the label and then you could distribute the product.

DR. LEE: Thank you, Pat. The next question, Pat

Gardner's slides inferred that adding components to another location is a CBE30. In the guidance document a change in components -- in conformance --

DR. DEVINE: In the guidance document a change in conformance with FDA guidance goes in the annual report. Why can't addition of a computer at a satellite location be included in an annual report, assuming the system is validated and implemented at the main facility?

DR. LEE: There are two questions. Mary, perhaps you are best equipped to address this.

MS. GUSTAFSON: Well, the second one first, I think Judy covered this in her annual report. You know, upgrading of a version of a computer system, or even actually putting the computer system in the satellite location could be in the annual report.

The other one -- let's see, Pat Gardner's slide -- that is adding a computer to another location. Yes, that is computer instead of component to another location. It is actually going from manual to computerized -- not being computerized and just adding a location of upgrading a version, but going from a manual to a computerized system. That is CBE30.

DR. LEE: Thank you, Mary. Here is one that is much simpler. When changing from one manufacturer to

another for infectious disease testing, i.e., from Ortho to Abbott, is this change considered a major change?

MS. GUSTAFSON: Judy specifically had that in her annual report. It actually, as far as your are concerned in your facility, is pretty much of a major change because you need to validate change of the test kit. But, from our view, we do review and approve all of the test kits. You are operating within the same type of test kit. They are all EIA test kits. We feel that you can validate that change appropriately under CGMP and it can be reviewed at an inspection. So, it could just be entered in the annual report, and it is quite possibly one of the changes that the field would want to look at extensively during an inspection.

DR. LEE: Another question regarding guidance documents. Guidance documents used to be minimum standards of practice. If they are non-binding, are they enforceable by FDA inspectors? If they are flexible, how do you keep track of what changes have been deemed acceptable?

DR. DEVINE: Guidance documents are not requirements. They do not outline requirements unless they are restating something that appears in a regulation or in a statute. Industry practices set the standard for good manufacturing practices. One of the issues with guidance

documents has always been enforceability. If the guidance document states something that is an industry standard or that is good manufacturing practices, and people that are expert in that area would agree with that in a court of law, then they are enforceable. But they do not set out requirements, as I said, unless, again, they repeat something in a regulation or in a statute. So, in that sense they are not enforceable. However, current good manufacturing practices are enforceable and those are scientific and technical issues that are usually worked out in courts and debated among scientists and individuals expert in that area.

In terms of if they are flexible how do you keep track of them, that is a good question. We have a type of industry that is constantly changing, and one of the ways to keep track of them is to currently keep them up to date and try to revise them as much as possible. You can see, for example, that the document we have already written and published in July is out of date for us. So it is incumbent upon us to expeditiously provide an alternative updated document. The best way to get the up to date information is, of course, to have an ongoing dialogue with your reviewers, and if you are not sure, then you can certainly call and ask.

In terms of how do you identify the most current documents, in the future under the good guidance practices the documents will clearly identify which documents they replace, and what the current revision is will appear in the Federal Register for a level I, which is an important guidance document.

Then quarterly there will be an update of all of the guidance documents and which ones are current. So, you can keep track of it through the Federal Register. Those lists will also appear on all of the centers' web sites. So, that is the way you have to keep up with it, and it is an ongoing challenge but that is the beast that it is.

DR. LEE: The next question is directed towards Mary Ann. If a center adds more stringent criteria questions to the donor history card, for example intranasal cocaine use, it used to be that it did not have to get prior approval and did not have to be reported. Does this now have to be reported in the annual report? I guess that is the gist of the question.

MS. DENHAM: The answer is yes.

DR. LEE: What is the anticipated turn-around time frame for PAS submissions? Depending on the nature, 6 or 12 months.

The next question is for Division of Hematology.

If you have a license for platelet pheresis products collected on the COBE Spectra and upgrade to the LRS, can you ship those products across state lines with the tie tag stating, "known to be collected by a process that reduces white count to less than 5 times 10^6?

MS. POINDEXTER: In discussions with Mary and others on the panel, the allowance of that tie tag was prior to our issuing the guidance document on leukoreduced products. We now have a memo out there for the people to abide by, so the tie tags that define the process and that it might be less than 5 times 10^6 or less than any other number should not be on the product if it is to be shipped across state lines as a platelet pheresis product that was previously approved, and it should not have the tie tag on it for within state unless it is absolutely necessary for the receiving people to know that they don't need to filter that product.

DR. LEE: Thank you, Betsy. The next question is kind of a generic one. What steps are being taken to ensure compliance with good guidance practices for the guidance currently under development, all blood and plasma guidances currently under development that relate to the BLA supplement issues?

DR. DEVINE: That steps that are being taken to

make sure that we adhere to the good guidance practices are that each of the centers has established standard operating procedures for how the guidance documents are developed and how they are cleared within the center. We have a standard operating procedure for CBER which defines what documents are level I and level II, and what the procedures are that people developing the documents in the Center have to follow. Each of the centers, namely the associate directors for policy, are monitoring the development and implementation. We are also being monitored at the level of the Agency as to how well we are adhering to these, and they are keeping track of our progress in this area. So, it is active surveillance within our own organization that has given us a handle on how well we are doing.

In terms of the lists, we are getting ready to publish our list of current guidance documents under development and those that have been published in the last quarter that are level II documents. I am not sure when that is going to be coming out. Do we know? It has to go through the Federal Register process and, that being a somewhat cumbersome process, I think it is supposed to be out in the next month or two. For the list for CBER, that will include all the blood and blood component documents under development, as well as all the other biologicals.

DR. LEE: Thank you. It says here a list of all blood and plasma documents as they relate to BLA supplement issues. Well, all guidances that are generated within the Blood and Plasma Branch, directed at the blood components industry, is related to BLA supplement. Obviously, the changes to reporting guidance is under preparation, as is the BLA.

I might add that there has been a guidance that has been in development for sometime, that is the autologous blood collection. It used to be a memorandum, and now is a guidance. That is under development. They had some legal problems associated with it which are close to being resolved. I can't think of anything in addition to that that we are currently engaged in. I am reminded of the guidance that provides how to collect two units from a single donor at a given setting.

The next question is to Dr. Devine. Should changes effected by FDA 483, which are told to FDA in response to that 483 be also reported otherwise?

DR. DEVINE: Yes, if you are going to make changes in response to observations listed on a 483, then you have to still comply with 601.12 and submit those changes in the proper category, either the PAS, CBE30 or annual report.

DR. LEE: Thank you. This one is for Mary. Can a

currently licensed blood bank get a supplement that would allow it to distribute blood collected by another blood bank not currently licensed?

MS. GUSTAFSON: If the currently licensed manufacturer wants to service the applicant and take the total responsibility for the unlicensed facility, functioning as a contractor under its license, and submit all of the relevant information under its license and maintain control of that facility, it is possible. But I would think very long and hard about it.

DR. LEE: Thank you for the comment. The next question has been directed to Judy. Please repeat your comments about facility changes which have occurred since the latest report. Did you state something about sending in a registration form within five days of opening? That is a very specific question.

MS. CIARALDI: Right. If there is one of those facility changes where there was a move or an addition that I had on my slide, the annual report may happen anywhere from 1 month to 11 months after the addition or the move takes place. We need to get that information into our computer, what the new address is and where you can now be located or where those facilities are now located. In order to do that, all you need to do -- and the registration is

separate from the licensure issues and it is always been that when you add a new facility or when you move a facility you need to submit a registration form within five days of the opening of that facility. That part has stayed the same. Now, saying that those types of facility changes have happened will go on the annual report. Our registration is filed separately from our annual report, and that is why it is really two separate functions.

DR. LEE: The next question is directed to Dr. Devine. Under the FDA Modernization Act, FDA is required to issue regulations implementing the new manufacturing changes section within 24 months. Should we assume FDA will repropose the recently finalized version of 601.12 for further comment to comply with this requirement?

DR. DEVINE: I don't think you should assume that. What is probably going to happen is that we are going to have to see what the Center for Drug Evaluation and Research is going to do and then we will make some decisions, once we know where that is going. However, we do feel that our rule complies with the new law in its current form. So, I don't anticipate that we would propose major changes to it. Whether or not we have to reopen the comment period is something that the lawyers will have to tell me, whether we have to do that or not. I am not sure of the answer to that

question.

DR. LEE: Thank you. The next question, what happens if we have a pending supplement and we do not notify FDA into which category we think the supplement falls?

MS. GUSTAFSON: If you don't notify FDA otherwise, we are handling all of your pending submissions as prior approval supplements. The question asks about pending, but in the future, because the new rule is meant to relieve the reporting burden for both you and for us, we will advise you, particularly if you submit things that should be in the annual report as prior approval supplements, we will tell you to, you know, save those type of changes and submit them in an annual report. For ones that could possibly be reviewed under a CBE30, we will at the time of approval tell you that in the future this is the type of supplement that could be reviewed as a CBE30.

DR. LEE: I believe these points have been made in the presentations but I will read them anyway. Industry would recommend that the Agency respond either by a receipt notification stamp or letter that the annual report has been received. Any comments about this?

The second part is does the annual report apply only to licensed blood products?

MS. GUSTAFSON: In answer to the first one, we

have decided that we will acknowledge receipt of the annual report, either through a letter or we might devise a stamp to stamp the front of the cover and copy it and send it back to you. We will not advise you that we have actually reviewed it -- completed a review and concur with it. We will advise you if things should be in a different reporting category. But in terms of have we received it, we will let you know in some form. We haven't quite figured out the way yet.

The annual report is only applicable to licensed manufacturers. The entire 601.12 rule are reporting requirements for licensed products. So, it is reporting changes to an approved application. So, I think because we had the other question about the annual summary, I think people are getting confused with the requirement for quality assurance where you do annual audits and you have annual reports of your audits, and you do a yearly review of your quality program. That is different than what we are talking about today, which is actually reporting changes to your approved application.

DR. LEE: Thank you. We are sort of on the home stretch here. The next question is not entirely clear to me, so if the person who posed the question is still in the audience, I would like to welcome additional input from the

questioner. For blood products, does the annual report fulfill the requirements of 21 CFR 211.180(e), or is something more required?

MS. GUSTAFSON: That is what I just answered. That is what I was afraid of, that there was some confusion. You know, they are totally different requirements. The intention is different. You know, they are under different rules. What we are talking about today is specifically the 601.12 regulation that outlines the way licensed firms report changes to approved license applications, period.

DR. LEE: Thank you for the clarification. The final written question is directed to Judy. Please explain why implementation of automated equipment for ADRH, syphilis and viral marker testing falls into minor changes instead of moderate changes. If the questioner would like to further comment and provide us with some rationale and background for posing the question, we would appreciate that.

MS. CIARALDI: If you think that it should be in a higher reporting category, you can make that comment and when we revise the guidance we will help you and, you know, bump everything up to a PAS. But, no, we thought that because of the length of the time that the industry has used this equipment and the lack of problems, pretty well people know how to validate and put these testing instruments on

line so that we could have it reported in a category that was downgraded from prior approval category.

DR. LEE: I have just been handed two additional questions. Should any particular FDA forms be submitted within the PAS or CBE30 and are major changes or CBE30 changes included in the annual report? I think this has been addressed, however, we may benefit from further clarification.

MS. GUSTAFSON: The first one is about the forms. You still continue to use the same forms that you are using now until the BLA is established.

MS. CIARALDI: I am sorry, I was writing. Was the question what form to use for the annual report?

DR. LEE: The question is are major changes or CBE30 changes included in the annual report also?

MS. CIARALDI: No. No, there is no double reporting. Annual report only covers minor changes. The major changes should come in as supplements, and you do not need to re-report them in the annual report.

DR. LEE: Thanks. When submitting annual reports, can PLA, ELA and labeling changes be reported separately when the ELA or labeling changes are across multiple products, i.e., adding a flag label for the pharmacy record -- I think this is not particularly applicable to this

particular workshop. If the questioner would like to further comment, you are welcome.

That concludes the written portion of the questions. If there are additional questions from the audience we would entertain them at this point.

AUDIENCE PARTICIPANT: I appreciate the opportunity to get some clarification on the FDA's thinking. What I think that I learned is if a question, for example the donor record question that was asked earlier, if the question is more stringent than what the FDA requires, then we can submit that as an annual report versus a PAS, if I understood that correctly. I was wondering could that same logic be applied to other areas of manufacturing with respect to other manufacturing steps? For example, if legal counsel recommends some modifications to our donor consent form with respect to a research protocol, and it is more stringent than what the FDA requires, could we apply the same logic? Another example might be the addition of an in-process control that is above and beyond what the FDA requires that we have established internally as a good step for assuring appropriate application of test results. I would like your comment as to whether or not a more stringent requirement would subject the firm to a PAS.

MS. GUSTAFSON: Generally, if it is more stringent

it can have a lesser reporting category, such as the annual report. I do want to caution that sometimes, if you are thinking of product enhancements or safety enhancement and you think, gee, this is going to make it more safe, like leukoreduction, when you are actually making an additional claim for a product that you market it will become a prior approval supplement. So, you kind of have to watch out and evaluate the change in terms of whether it makes an additional labeling claim or changes the product in any substantial way. If it truly is putting in an in-process control that is more stringent or certain additional questions that we don't require on the donor history form, that can be under the annual report.

I would add that in future guidance documents where we recommend certain screening questions or actually give verbiage to be used in a question -- in fact, we have one in process right now -- we are going to try to include in the guidance document what the reporting category will be for the licensed establishments. So, we are going to try very hard when we issue a guidance document to let you know if licensed establishments can report in the annual report way.

AUDIENCE PARTICIPANT: Hi. I just have a comment. I really appreciate this forum for furthering understanding

of what you are expecting of us and better communication back and forth. I just have a comment, and I don't know how many people I speak for that are here today but I have discussed this with many, many people from my part of the country, and I have worked in three different blood centers over the last ten years, and in all three settings looking at how these things are going to be applied, I am at a complete loss to understand how this falls in with paperwork reduction or less work, more streamlining in the blood and blood components industry. It is going to be a tremendous impact on me and my job right now, and would have been in the other two positions I have held. There is going to be a lot of new reporting for our industry. I don't know if it may be cutting down in other areas and other industry. But I don't see, and no one I know can tell me where there is anything being cut. I only see a tremendous amount of new things being added, and I don't see where we are furthering blood safety by you wanting to know if the donor chair is on the north wall and has been moved to the south wall, or that this temporary wall in the lab has been moved over to this place. It has nothing to do with the testing itself or so on. There are so many examples of that -- I am at a loss.

MS. GUSTAFSON: if a firm was adhering to the old 601.12 reporting requirement, which required that every

important proposed change be reported to the Center and all of those changes in methods of manufacturing and labeling needed to be approved prior to implementation -- if a firm was actually adhering to the letter and spirit of that regulation, this is a decrease in reporting.

We do know that over the years, and we have had comments, there have been licensed blood establishments that have not been reporting and have been getting away with it. But we also have many, many licensed establishments that have been over-reporting over the years, and this will in fact reduce the reporting burden.

Some the examples today maybe were a little bit overplayed, and I think if we can get your comments on the specific things that you think should not be subject to any reporting at all, that are so minor that they don't even fall into annual reporting, we would welcome those comments as we move along in developing the specific guidance.

DR. DEVINE: I would just like to add one other thing to that burden reduction question, and that is part of the tradeoff in terms of the downgrading is you no longer now have to wait for approval for many of the important changes that you did under the previous regulation. So, part of the burden reduction is your ability to use and implement the change much sooner which, hopefully, provides

for a better product and more efficient operation for your facilities.

So, when we look at burden reduction we don't just look at the amount of paper submitted but we look at the overall benefits for the industry, the Agency and the continued protection of the public health, which has to be weighed in into all of that. So, we did burden estimates that were based on, as Mary said, if people were complying with the old regulation. We have heard from a number of people that maybe they were not quite clear about what the requirements of the previous regulation were. So, I would reemphasize that if you were complying with that previously, all of these things which are now listed in CBE30 and some of those in the annual report category would have been prior approval supplements under the previous system and now you are submitting maybe an annual report, which is less information than is in a supplement; it is more abbreviated and summarized; but you also now have the availability of being able to implement the change at a much earlier date.

So, that is how we look at the overall burden reduction. For us, the collapsing of information into an annual report that was previously in separate supplements saves us a lot of time in processing in paper because each supplement that came in had a tracking number assigned to

it. It had a letter generated from it. It had to be routed by secretaries; it had to be read by reviewers. You now have one annual report which contains multiple things that would have been processed separately. For us, it is truly a paper and processing burden reduction.

So, it may not be crystal-clear to everybody how much the benefits are really there but I think you will also see even more when the BLA is collapsed into the single submission. I think you will see a dramatic reduction in the number of filings that you have to make. There may be a little bit more information consolidated into these, but I think you will see an overall burden reduction.

AUDIENCE PARTICIPANT: Hi. Could you please clarify for me if a licensed blood establishment uproots from its current facility into a new building, a totally new building and it does manufacturing, it does testing, it does distribution, is that a CBE30 or a PAS?

MS. GUSTAFSON: By uprooting, do you mean you are moving to a new facility?

AUDIENCE PARTICIPANT: Yes, a relocation.

MS. GUSTAFSON: Right now we are still issuing the little certificates that say where your locations are. So, I mean if it is in a neighboring town and we have to issue a license, I think we have it under a CBE30 but we would have

to issue a license. We would consider that a CBE30 for a facility move.

AUDIENCE PARTICIPANT: Okay.

AUDIENCE PARTICIPANT: I am afraid I must agree with the previous speaker who suggested that this is going to create a mountain of paperwork for us. I think few of us would disagree that the kind of changes you propose being reported in the top two categories are certainly the things that we are accustomed to. However, the items that I have seen listed in the annual report, I think many of those I would argue about their importance, and that will create a significant burden to us, not only in preparing the report for you but in accumulating information from the various departments in which they occur.

DR. DEVINE: Again, we would ask you to make those comments to the docket in writing, and be very specific about the ones on the list that that you think should be downgraded and we will take it under consideration. That is part of the reason why we put the draft document out for public comment. I think we would venture to say that we got very few specific comments about the lists of information on the guidance documents when they were issued in draft. Nevertheless, at this point we are certainly prepared to reconsider. So, please do submit it and be specific and we

will be happy to take it under consideration.

AUDIENCE PARTICIPANT: The issue of computer software upgrades has been touched on a couple of times. I just want to be sure that I understand exactly the FDA position. Clearly, a software change could impact the safety of blood as it is released. Am I to understand that that is excluded from this, a change that might include validations and SOP changes?

MS. GUSTAFSON: No, we had that as a CBE30, if you go from a manual to a computerized system. Once you have actually moved to a computerized system and you know how to validate a computer system, we feel that you are trained and that if you need to upgrade or change to another vendor that that could be handled in an annual report.

Also, that is teamed with the fact that we now require software vendors to submit 510(k)s to us for clearance. So, we have a balance with those changes.

AUDIENCE PARTICIPANT: Okay, and our software will have quarterly software upgrades. That will not require a comparability protocol? That will simply be part of the annual report?

MS. GUSTAFSON: Is this vendor supplied software?

AUDIENCE PARTICIPANT: Yes, and it is mandatory.

MS. GUSTAFSON: No, you can report the change,

whatever versions and the date that you implemented the change in your annual report.

AUDIENCE PARTICIPANT: Thank you.

AUDIENCE PARTICIPANT: I would like to ask another question about the facility relocation. If a portion of the functions of a facility relocates but none of the donor collection, donor suitability, manufacturing portion relocates, is that an annual report or a CBE30? For example, if finance, donor recruitment, information systems moves to a building next door?

MS. GUSTAFSON: I think we would be happy with an annual report on that one.

AUDIENCE PARTICIPANT: Thank you.

AUDIENCE PARTICIPANT: The regulation reads that for annual reports, data results from studies and tests performed to demonstrate the minimal impact of the change are to be in the annual report. Have you given any thought to what data you are looking for or how highly summarized it could be? Or, are we talking about annual reports that are perhaps volumes long?

MS. GUSTAFSON: We don't want volumes and we don't think that you want to send us volumes. Basically, the types of things that we need to flush out are in the guidance and, actually, your input is extremely important to

us in developing some of the future guidance.

DR. DEVINE: And keep in mind that the regulation applies to more than blood and blood components, and it does say relevant data. So, you know, some changes are pretty straightforward, changes in personnel for example. So, it is relevant data and you have to assess it based on the type of change in the product. It is written broadly, and I think format is an issue for the annual report, not just for blood and blood components but we are anticipating for other biologicals some guidance on the content and format of an annual report.

AUDIENCE PARTICIPANT: Maybe I am confused and before I leave I am hoping to get this right. A donor center, whether it be collecting plasma, whole blood or either/or, what category would that fall into if it relocated?

MS. GUSTAFSON: In terms of relocating -- you are from the plasma industry -- right now it would be a relocation move and you would need to submit an ELA. I think we had it under a CBE30 for now. Like I said, in terms of developing the guidance, we need to roll in the fact that we are converting to a BLA and how to actually handle the facilities in a better way, in a clearer fashion in our next guidance document.

AUDIENCE PARTICIPANT: But that is only if you don't change towns. Right? If a new license has to be issued, then it is a PAS? Is that how it works?

MS. GUSTAFSON: It is a CBE30. We do have to approve it but we will let you make that change before we actually approve it.

AUDIENCE PARTICIPANT: Just listening to your last response, if it is a blood establishment and we move within the next couple of months, then I have to submit an ELA plus the CBE30?

MS. GUSTAFSON: It would be filed as a CBE30 under the changes to be reported, but it would require your ELA/PLA filing, just as you have been doing because we have not yet converted to the BLA.

AUDIENCE PARTICIPANT: Okay.

MS. GUSTAFSON: Last question!

AUDIENCE PARTICIPANT: It is an easy one. I want to thank you for letting us sort of badger you because it is very nice to have this open forum, but I want to ask where we should send the written comments. I agree with a couple of the other speakers that this is going to triple my work, and I realize that you have had your comments but you said that you would still be open to more comments. To whose attention? To yours, Mary?

MS. GUSTAFSON: I think the best thing to do is to wait for the CMC guidance to publish the notice of availability of the guidance document, the one that Gil went through this morning, and publish the comments to that docket. No, I am mixed up; it is getting late in the day here! It is still an open docket for the guidance documents that were issued relative to the 601.12 final rule and that is where you should submit the comments for the guidance on the changes to be reported.

DR. DEVINE: The docket number should be on the front of the guidance document. It is also in the Federal Register notice. The Federal Register notice is available on line either through the Federal Register web site or through ours, and you can get the docket number there. If you are not sure where to send it, you can always call our congressional consumer affairs group and they can give you the answer, or you can call our regulations and policy staff and they can give you the docket number if you don't have it.

AUDIENCE PARTICIPANT: Thank you.

DR. DEVINE: It is in Tab 13, and the address where you send it is also in there.

AUDIENCE PARTICIPANT: First I would like to say that I think this was a very effective workshop and that the

handout was very beneficial. It is going to be very helpful us in preparing these applications.

I have one question and a couple of things I need clarification on. I will be very quick. Once a comparability protocol requesting a change at multiple sites is submitted and approved, why is it necessary to continue to submit facility-specific supplements if no additional facility-specific data is required? I see this as a way to save paper and I don't see any real value added to continue to send these supplements when you are getting no new or site-specific information.

MS. GUSTAFSON: Well, there may actually be site-specific information. We may want to see your QC data for the individual sites. It would depend on what the change is. That is why the comparability protocol needs to be developed specific to a change within an applicant's facilities. There may be some roll-outs that we might not need to see. We may just say in your annual report list what days the facilities came on line with this change. But if there are data that we would want to review, I would imagine it would be a CBE30.

AUDIENCE PARTICIPANT: Thank you. I have a question pertaining to when to submit the annual report. If a manufacturer's initial application date is prior to

October 7, 1997 -- say, it is October 6, when would that annual report need to be sent? It would be 60 days from the October 6, 1997 or would it be a year? It is not clear to me.

MS. CIARALDI: That falls under the second slide. The first slide talked about the anniversary date between October 7 and January 20. The next slide talked about the anniversary date on or after January 20, which would be your October date.

AUDIENCE PARTICIPANT: No, prior to. What if it is before October 7, 1997?

MS. CIARALDI: There is no prior to, because it is when the rule became effective.

AUDIENCE PARTICIPANT: So, the first supplement is submitted after October 7?

MS. CIARALDI: Right.

AUDIENCE PARTICIPANT: All right. For example, on the letter we received the date was 1950. So the first supplement submitted after October 7?

MS. CIARALDI: It would be on that month and day but corresponding to the information on the slides as to whether it would be in 1998 or January, 1999.

AUDIENCE PARTICIPANT: Thank you. If you are opening up a new donor center where you have pheresis and

whole blood, if I understood you correctly, it would be an annual report to open the center but to license the product you would need to send in a PAS?

MS. GUSTAFSON: That is right.

AUDIENCE PARTICIPANT: Okay.

MS. GUSTAFSON: Don't forget to register your center.

AUDIENCE PARTICIPANT: Right, so you need to send in the registration form, which probably leads to my next question, if you have an annual report type of submission and we submitted it as a CBE30, even though it can be submitted as an annual report with the understanding that it can be submitted as an annual report, is that acceptable? To me, it doesn't make sense to send in a 2830 and then have to go through that same process down the road. I would just as soon send it all in at the same time. Your answer was that we could do it but you would notify us that this is a lower reporting category. My question is can we report it at a higher category?

MS. GUSTAFSON: We will, at some point in time, start bumping it down because of the burden on us to review those pieces of paper. This is intended to reduce the burden on us as well as you. But Mary Ann offered to talk to you tomorrow if you want to call her.

AUDIENCE PARTICIPANT: Just one final comment, I do appreciate the fact that these new regulations help us get product to market faster, and I do understand that and it is very important to manufacturers. But I think I have to agree with some of the other commentors who said that they don't see any real paper reduction, at least from the manufacturers' point of view. I honestly don't see the degree that you are talking about but I do see the benefits. So given the trade, I will take what is happening. Thank you.

MS. GUSTAFSON: Let it mature, and I think, as Dr. Devine mentioned, you will in time see a reduction. Right now it looks fairly onerous, particularly if you paid no attention to the rules on reporting earlier. But I think in time this will mellow out. As we become more familiar and comfortable with the new reporting, I think we will downgrade more things.

We are down to a dwindling few. There have been thanks all around today, but I want to thank all of you for coming and staying until this later hour. I particularly want to thank this woman on my left, who is Dr. Becky Devine, and she is the Associate Director for Policy for the entire Center for Biologics, and Dr. Bob Yetter, who is on her policy staff. They really blocked out their entire

calendars to be with us today for this workshop, and I think it shows you the commitment from our Center manager for the Blood and Plasma Program, and I do thank you for being here, and thank all of you.

[Applause]

[Whereupon, at 5:05 p.m., the proceedings were adjourned]