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Center for Biologics Evaluation and Research

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P R O C E E D I N G S (12:00 p.m.)

Agenda Item: Opening Remarks/Introductions

DR. JACKSON: Good morning, everyone. I would like to welcome everyone to the 105th meeting of the Blood Products Advisory Committee. I'm Brooks Jackson, the new chair of this committee. I would like to welcome everyone and thank everyone for taking time out of your busy schedules to attend this important meeting, which really is a public service.

I would like to first to introductions, if that's okay. I think we have only one person who is still due to arrive. If you could start by telling us who you are, what your affiliation is, and what your expertise or area of interest is, I think that would be helpful. I'll start.

I'm Brooks Jackson. I'm professor and chairman of pathology at Johns Hopkins University. I'm a board-certified blood banker and do research in the prevention and treatment of HIV, hepatitis, and TB, primarily.

DR. SCHEXNEIDER: I'm Katherine Schexneider. I'm a commander in the US Navy. I'm the transfusion consultant at Walter Reed Bethesda, right down the road. I'm also a pathologist and fellowship-trained transfusion medicine physician.

DR. STOWELL: I'm Christopher Stowell. I'm the medical director of the Blood Transfusion Service at Mass

General Hospital and an associate professor of pathology at Harvard Medical School.

DR. SIMON: I’m Toby Simon, senior medical director at CSL Behring, with an interest in pathogen safety of plasma derivatives and coagulation and hematology. I also do have a background previously in transfusion medicine.

MR. DUBIN: I’m Corey Dubin. I represent the end-user communities and, as we like to say, I have an arm in the game. I infuse the products that you work on and manufacture. I was the first guinea pig at Highland Laboratories in the 1960s for factor concentrate, so I was 001.

DR. PIPE: I’m Steve Pipe. I’m a professor of pediatrics and pathology, University of Michigan. I direct the Special Coagulation Laboratory and the Hemophilia A Treatment Center.

DR. MAGUIRE: I’m James Maguire. I’m at Brigham and Women’s Hospital, professor of medicine at Harvard Medical School, infectious disease specialist with interest in parasitic diseases.

DR. KUEHNERT: I’m Matt Kuehnert, director of the Office of the Blood, Organ, and Other Tissue Safety at CDC. I’m board-certified in infectious diseases and don't have a lot of expertise in antigen typing, although we do have a

hemovigilance program, and so some of the issues that we'll discuss will probably be relevant to that in terms of errors that occur in the hospital setting.

DR. GILCHER: I'm Ron Gilcher, emeritus medical director of the Oklahoma Blood Institute, now in private hematology and immunohematology, transfusion medicine consulting.

DR. LEITMAN: I'm Susan Leitman, chief of the Blood Services Section at the Department of Transfusion Medicine at the NIH Clinical Center, just three miles south of here. Training is in hematology and oncology and blood banking. I have spent the last 25 years of my professional life in transfusion medicine.

DR. DURKALSKI-MAULDIN: I'm Valerie Durkalski-Mauldin. I'm a biostatistician at the Medical University of South Carolina in Charleston.

DR. BONILLA: Francisco Bonilla, Division of Immunology, Boston Children's Hospital and Harvard Medical School. I'm a clinical allergist/immunologist. I focus on immune deficiency.

DR. JACKSON: Thank you, everyone, and welcome again.

This afternoon we will start off with several presentations that will frame the issue for discussion today. We will take questions, one or two, after each

presentation, and then we will take a break.

Before we start, I think Bryan Emery would like to read the conflict-of-interest statement and go over some housekeeping issues for the meeting.

LCDR EMERY: Hi. Welcome, everybody. I'm Bryan Emery. I help to run the Blood Products Advisory Committee. I am the designated federal official.

(Administrative announcements)

At this point I'm going to read the FDA conflict-of-interest disclosure statement.

The Food and Drug Administration is convening the December 4 and 5, 2012 meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all participants of the committee are special government employees or regular federal employees from other agencies and are subject to the federal conflict-of-interest laws and regulations. The following information on the status of the advisory committee's compliance with federal ethics and conflict-of-interest laws, including but not limited to 18 USC 208, is being provided to participants at this meeting and to the public.

FDA has determined that all members of the advisory committee are in compliance with federal ethics

and conflict-of-interest laws. Under 18 USC, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Related to the discussions at this meeting, members and consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 USC 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For Topic I, the committee will discuss and make recommendations on labeling of red blood cells with historical antigen typing results. This is a particular matter of general applicability.

For Topic II, the committee will discuss performance data considerations for infectious disease assays used to screen organ donors. This is a particular matter involving specific parties.

Based on the agenda and all financial interests

reported by members and consultants, no conflict-of-interest waivers were issued under 18 USC 208.

Dr. Toby Simon is serving as the industry representative acting on behalf of all related industry. Dr. Simon is employed by CSL Behring in King of Prussia, Pennsylvania. Industry representatives are not special government employees and do not vote.

There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest.

This conflict-of-interest statement will be available for review at the registration table.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise

the committee of any financial relationships that you may have with any firms, its products, and, if known, its direct competitors.

Thank you.

DR. JACKSON: Thank you, Bryan.

The topic, as you know, for this afternoon is the labeling of red blood cell units with historical antigen type results. To introduce the topic and the FDA perspective, Jennifer Jones will give the first presentation. We'll have probably time for one or two questions afterwards. I think we should be on time.

Agenda Item: Topic I: Labeling of Red Blood Cell Units with Historical Antigen Type Results

Introduction and FDA Perspective

MS. JONES: Thank you.

We're here today because FDA is seeking advice from the committee on appropriate practices for labeling red blood cell units with historical red blood cell antigen typing results. In particular, we seek to examine current practices and to be advised as to candidate regulatory standards, because we are aware that within industry there are varying practices that are used to perform the antigen testing. During my presentation today I'm going to be covering those different practices, and then we're going to really focus on the labeling when it's done using

historical test results.

For today, I'm going to start by going over a background and overview of the antigen typing process. I'm going to discuss some of the current practices that are used for locating antigen-negative units. Then I'll discuss some of the current FDA considerations on this topic and then present some labeling with historical antigen results, some of the different processes that are used in other countries. Finally, we'll have the questions for the committee.

With the background information, I'm going to start at the time of donation in a blood center. A donor is going to present to donate. At that time, a donor number will be assigned that is specific to the donor after the donor has presented identification. Currently there are no standards to verify identity of the donor. Sometimes a donor may present a driver's license. The donor may just have any form of picture ID. They may have to present a Social Security card. Within industry, there are varying practices to establish the donor identity.

After the donor has been assigned the donor number, donor suitability of the donor will be determined. The donor will be asked questions, and there will be a mini-physical exam performed. Then a unit number is going to be assigned to the specific collection for that donation

on that day for the donor. Any applicable paperwork or donor records, the blood bag, as well as the sample tubes are all going to be labeled with that specific unit number for that collection.

So basically we have linkage traceability on the donor records, the donor, the blood bag, the sample tubes where specimens will be drawn for infectious disease testing. Finally, the unit is collected from the donor.

I have presented a very simplified overview of the process when the donor presents to donate.

Once the unit has been collected, the required ABO and Rh typing is performed, along with the infectious disease testing. At the conclusion of testing, a final printed label is going to be applied to the blood bag. On that container label it will have the collection facility information, the product name, the blood type, and the expiration date.

In order to obtain that label that goes on the unit of blood -- it may be a computer-generated label, but having a computer-generated label is not mandated by FDA, so there are other methods. It could be a computer-assisted process, in which there could be a preprinted label, but the facility is using a computer to pull up the donor records and they are scanning the unit number, or it could be an entirely manual process, where there’s no

computer that is used in doing the labeling. You are using paperwork and then verification by different technologists. There’s no computer involved.

Once the unit has been labeled, it is then placed into inventory.

This is just an example to show what a container label looks like. This is a widely used label within industry that is standardized and meets FDA regulations. In the upper left-hand quadrant is the facility information. That long barcode where you have the W00 would be the unit number that is assigned to this collection. In the upper right-hand quadrant is the ABO and Rh typing. The lower left-hand quadrant contains the product information. The lower right-hand quadrant is going to have the expiration date and any additional information that is going to be printed pertinent to the unit.

It’s important to note that the information is machine-readable. But in addition, the barcode text is encoded into the barcode as well. For example, if you look at the lower right-hand quadrant, this barcode is relevant to the product code, and encoded in that information is that this unit is red blood cell and it includes that it’s collected from 450 mL CPT whole blood and the storage information.

In addition to the standard ABO and Rh, there are many non-ABO red cell antibodies that exist in the general hospital population, as well as the chronically transfused. It’s these non-ABO antibodies that may be capable of causing hemolytic transfusion reactions. Routine compatibility testing does include procedures that detect clinically significant red blood cell antibodies and provide blood that lacks the corresponding antigens.

In order to perform the antigen testing, the blood establishments, whether a blood collection center or a transfusion service, use licensed reagent antisera to perform the antigen testing. With licensed reagent antisera, it’s a reagent that has been reviewed by FDA according to good manufacturing practices. But if there’s no licensed reagent antisera available, blood establishments may also use unlicensed antisera with appropriate positive and negative controls. An example of an unlicensed reagent antiserum could be an in-house reagent that the firm has developed or it could also be expired reagents that the firm is still using. They can use those with the positive and negative controls.

Some blood establishments also use molecular methods to determine RBC phenotypes, but currently there are no FDA-approved molecular test kits available.

When you’re performing the testing, one of the

most important things is to establish linkage and traceability between the donor and the unit number. The records must relate the donor with the unit number of each previous donation from that donor. The linkage should be traceable both forwards and backwards. You should be able to take a donor and trace the record trail down to the unit or you should be able to take a unit and be able to trace it back through the records to that donor as well. Some blood establishments will achieve this linkage and traceability by using a blood establishment computer system.

It is possible to have duplicate donor records exist, so there should be a process in place that would detect these duplicate donors. For example, if a donor presented to donate with a new name -- for example, if I was Jennifer Jones and now I'm Jennifer Smith -- if I presented to donate as Jennifer Smith but I don't inform the blood center that I had a name change and they don't ask the questions that identify that I was previously Jennifer Jones, all my units are now going to be associated with Jennifer Smith rather than Jennifer Jones. So now I would have essentially a duplicate record with that facility.

To this point, I have talked about the donation process at the blood center and talked about the importance

of having the records linked to the donor and the unit. Now I would like to move into talking about some of the current practices for locating the antigen-negative blood.

I'm going to use the example that a transfusion service has identified a patient that was requiring blood that is negative for both the E and Kell antigens. In this situation, if the blood establishment -- either the blood collection center or transfusion service -- determines that they have no units that were previously typed as negative for the red cell antigens E or Kell in their inventory, they are going to select random units on which to perform the testing. They may select 10 to 15 units and then perform testing on those units to try to find an E- and Kell-negative unit. The antigen typing will be done with one antiserum for each antigen. Out of that first batch of testing any units that are negative will be antigen-typed using an antiserum from a different source, if it's available. Finally, the end result would be, out of both of those sets of testing, any units that test negative are going to be labeled as E- and Kell-negative.

In this first example we're performing testing on the current donation.

Using this random testing method, there are some challenges that are associated with it:

- It may be very time consuming.

• It is labor- and resource-intensive. As I said, for example, the establishment might be choosing 10 or 14 units, so they are using reagents on all of those units, out of which they may just find three that are E- and Kell-negative.

• The first may also lack the appropriate antisera.

• It is possibly difficult to complete this random testing in emergency situations.

• It can be very expensive for the establishment.

The second method I would like to discuss is when historical RBC typing results are used to identify appropriate units to test. At the blood collection center the staff may pull an inventory report to locate units from donors who in the past have typed as E- and Kell-negative. Once they have identified those donors, they are going to pull units from those donors that they have in inventory and on those units they are going to reconfirm the E- and Kell-negative units. Again, this testing is performed on the current donation. Once the testing is complete, the units will be labeled as E- and Kell-negative.

In The two examples that I have provided the antigen testing has been completed either using the random testing or using the historical results to identify donors who previously typed as negative. Once testing is

completed, the unit is going to be labeled, either on a tie tag, with information on tie tag, or the container label. In both of these examples that I have discussed, the labeling is based on tests performed on the current donation.

This is a picture of a blood bag with a tie tag attached. Here you can see the phenotype information, the E and the Kell, as indicated on the unit.

This is the same example of the label that I discussed earlier, but here in the lower right-hand quadrant, the phenotype information has actually been printed on the barcode and it could be encoded in that barcode. This is phenotype information based on tests performed on the current donation.

Once the unit has been labeled, the unit is now ready for distribution. We're going to move into pre-transfusion testing. The unit is either already at the transfusion center or the blood collection center. Now that they have completed their testing and labeled the unit, we'll send the unit to the transfusion service. In some instances the transfusion service will receive the antigen-typed unit from the blood collection center. If that happens, the transfusion service may repeat the antigen typing to confirm that the unit is antigen-negative. But in all cases a cross-match is going to be

performed prior to transfusion. However, if there is an emergency situation, a cross-match may be performed after the transfusion. It may not be possible to perform it before the transfusion.

Finally, aside from an emergency situation, after the cross-match has been performed, the unit will be issued for transfusion if all testing discrepancies are resolved and the cross-match is compatible.

The compatibility testing is done to ensure the safest possible product for the recipient. This is an overview of the different steps that are involved in compatibility testing. There will be a review of the patient’s past blood bank history and records, if they are available. This is one example of an area where it’s important to ensure that you have adequate linkage and traceability of the unit to the correct donor records, since you are reviewing the patient’s past history. Then ABO and Rh grouping will be performed of both the recipient and the donor, then antibody screening of the recipient serum, and finally, the cross-match is performed, which is the final check of ABO compatibility between the donor and the patient. The cross-match should detect the presence of an antibody in the patient’s serum that will react with antigens on the donor’s red blood cells.

At this point everything that I have been

discussing -- the antigen testing that has been performed -- is testing that has been performed on the current donation. But there is an alternative practice for providing antigen-negative blood. That is when some blood establishments provide red blood cell units with red blood cell antigen typing results from previous donations, which we'll call historic results, without performing testing on the current donation. This is what we're here today to discuss at BPAC, this alternative practice, if you will, using the historical results.

The transfusion service may or may not confirm the antigen typing on the current unit.

There are different methods that are used to convey these historic results, that blood centers use to convey them. The first is a shipping invoice. A shipping invoice may be included with the red blood cell units and it would include the historical antigen typing results of any units within that shipment, and it would state that they are historical results.

There could also be a separate document that would be included in the shipment, but it would contain the same information that might be placed on a shipping invoice.

The third method would be a tie tag that would be attached to the red blood cell unit. It could be a tie tag

like I showed you in the picture earlier in the presentation, but rather than stating that tests performed on the current donation, it would list the historical red blood cell antigen typings and identify them as historical results.

With all of these different types of situations, the information is typically based on two historical test results.

In summary, there are three different practices that I have discussed for providing the antigen-negative blood. The first, as I called it, was method 1, which was random selection of units for testing. That was based on testing performed on the current donation. The second method was using historical red blood cell antigen typing results from donors to identify appropriate units to test. Again, labeling is based on tests that are performed on the current donation. Finally, there’s the alternative practice, which is directly using historical results and labeling the unit without performing testing on the current donation. It’s this alternative practice that we’re going to be discussing for the afternoon, with all the different presentations today.

There are some FDA considerations that I would like to go over concerning the use of the red blood cell historical phenotype. Industry has conveyed the following

information through AABB to FDA. There are blood collection centers that perform RBC antigen typing either serologically or by a DNA-based method. It is the practice of many blood centers to provide that information, the testing results, to the transfusion service. As we have discussed, there are some blood collection centers that include the results on a shipping document or on a tie tag attached to the unit or on a report that is included with the shipment.

Prevalent industry practice is to label a red blood cell unit with RBC antigens based on tests from the current donation. This industry practice would be the two methods that I described earlier, the method 1 or method 2, random selection or selecting units based on historical results from the donor.

But there are some blood establishments that are proposing to label current collections with the results of RBC antigen testing from previous donations. We'll call this historical results on the donor. This method is what I discussed today as the alternative practice that exists. It is important to note that with this alternative practice, or this second bullet that I'm discussing, using the historical results, the transfusion service may or may not confirm the antigen typing on that unit. It's those units in which the antigen typing is not confirmed that are

of most concern.

FDA does have some concerns about the process of using the historical results. The first is accurate linkage of the donor's historical antigen test results to the current donation through a positive identification of the donor. You could have an incorrect donor -- for example, duplicate donors that I discussed earlier. You may have a unit that does not get linked to the correct donor. You could have two donors with similar names. You could have Jennifer A. Jones, Jennifer M. Jones, and if I present to donate as Jennifer A. Jones but my collection gets linked with Jennifer M. Jones, then you are not going to have the appropriate traceability back to the records of Jennifer A. Jones that you need.

You could have sample tubes that are not linked to the correct donor. There could be test result data-e entry errors of the antigen typing results. There could also be labeling errors that may occur.

Another concern is whether a need exists to confirm the historical antigen test results on the current donation, either by the blood collector or the transfusion service. There could be errors in testing that may occur, in which case it would be prudent to have confirmation at the transfusion service.

Another concern is assurance of the quality of

the antigen typing results.

Through this process of AABB conveying the information from industry to FDA and FDA expressing our concerns, AABB did create a workgroup with members of industry, as well as FDA liaisons. The workgroup is charged with exploring the current and anticipated use of historical antigen typing and developing an industry position statement. Rebecca See, who is chair of the workgroup, is going to review the workgroup structure and activities later today during her presentation.

There was an informal survey that was conducted. From that survey, it has become evident that there are other countries that do use historical RBC antigen results in differing scenarios. On this slide I have two of the processes listed. The issue summary that was provided has a more detailed chart with a lot more information on other countries, other than those I have listed on this slide.

One process is to use a system of different formats. You could have regular, bold, and underlined text to indicate if the phenotype has been tested once or twice and on two different donations. This process is used in Canada, Australia, and Israel. Later today we'll hear from Dr. Goldman, who is going to be presenting more information on this process used within Canada.

Another process is to only label with historic

phenotypes after the donor has been tested on at least two donations. This process is used within the Netherlands, Australia, and Hong Kong.

Again, this is just a sampling of some of the different processes.

There are some benefits of labeling when you use only historical antigen results. It does allow the transfusing facilities to preselect antigen-negative units for compatibility testing. This could become important in an emergency situation or situations where you have chronic transfusion support. It is likely to reduce errors if the donations have been tested more than once and if the correct units are selected. It can save time and resources and may minimize the use of antisera and other reagents that are sometimes in limited supply at the blood establishments.

But there are also potential risks that may occur with labeling using only historical antigen results. The primary would be a hemolytic transfusion reaction. This could be due to transfusion of a mistyped or mislabeled unit -- for example, if there’s an inadequate process to ensure linkage of the current donation to the historical results or if there’s an incorrect result or weak reacting antisera. This is one reason why it becomes very important to ensure that there is adequate linkage from the donor and

their historical results to the units. Reconfirming the antigen type prior to transfusion may mitigate this risk of a hemolytic transfusion reaction.

Within FDA, there are some typing errors that have been reported to FDA from blood establishments through biological product deviations. If there’s an error that occurs once a licensed product has been distributed, the firm must report that error to FDA through what is called a biological product deviation. They will provide a description of the error, the cause, and so forth. We were provided some of this information. I have chosen a few of the examples in which typing errors have occurred.

With the first example, there was a component that was incorrectly typed and labeled as Kell-negative by the reference lab. Then it was sent to the transfusion service, and upon repeat testing by the transfusion service, the unit was confirmed as Kell-positive. At this blood establishment, they returned the unit to the reference lab, which also confirmed the unit as Kell-positive. The blood establishment reported the cause as an error attributed to the medical technologist.

This is one example where, at this facility, if they were using historical antigen results to label the unit -- it is good that in this case the transfusion service was confirming these units, because they caught the

error and they confirmed that it was Kell-positive. The unit did not get transfused, so there was no possibility in this case of a transfusion reaction occurring, because the error was caught.

The second example is a red blood cell component that was incorrectly typed and labeled as P1-negative. The cross-match was compatible, and this unit was transfused. A transfusion reaction was reported by the blood establishment. Repeat testing showed by the reference lab confirmed the unit as P1-positive, not P1-negative. In this case the firm reported the cause as the tech failed to check if the P1 antiserum was in the test tube prior to adding the donor’s red blood cells at the time of antigen confirmation.

This is an example of -- as I talked about earlier, this could have been a typing error. That’s the information that we were provided. I talked about that earlier.

The last example I have is a red blood cell unit that was tagged incorrectly as negative for the Kell antigen by the collection center and distributed to the transfusion service. At the transfusion service they tested it as Kell-positive and returned it to the blood collection center. The repeat testing there also showed it as Kell-positive. The firm reported that they had

inconsistent results from their Kell antisera. This could potentially have been an example of weak-reacting antisera or it could have been a methodology with the test. We're going off of the information that was provided to us.

So these are just a few of the examples that have been reported to FDA where you can see that errors have occurred within the typing process, the typing results, or linkage to the donor.

Labeling units with red blood cell historical antigen results may convey logistical and safety advantages in the transfusion setting. But it may be associated with additional risks as well. Questions do arise regarding the accuracy of the historical results and linkage of those results to the current donation. In some countries do permit labeling with historical red blood cell antigen typing under several differing scenarios, which I presented today.

Questions for the committee today that we would like to discuss: Please comment on the effectiveness of the following practices to mitigate the risks related to historical antigen typing. The first is reporting such information on the basis of historical red blood cell typing results from two separate donations, a validated process to confirm donor identification and accurate linkage of the current red blood cell donation to the

historical results, and confirmation of relevant negative antigen results on the current unit prior to transfusion, when feasible.

The second question we have today is: Please comment whether your responses to the first question would vary if serologic or molecular testing or both are performed.

Our agenda for the rest of the afternoon: Next, Dr. Katz will be discussing the blood center perspective, followed by Dr. Uhl, who will talk about the transfusion service perspective. Then Dr. Denomme is going to talk about red blood cell genotyping within the blood bank setting. Dr. Goldman will go over the processes that are used within Canada for historical labeling. Finally, Rebecca See will be talking about AABB workgroup and the activities that have gone on within that workgroup and the present status.

DR. JACKSON: Thank you, Jennifer.

We have time for one or two questions. Susan.

DR. LEITMAN: Jennifer, is it a regulator requirement for centers to report to FDA through a BPD, a biologic product deviation, if a unit is returned because there was incorrect typing reported, so that FDA can keep track of such events?

MS. JONES: If the unit has been distributed --

and I will defer to other people to jump in -- if the unit has been distributed and has left the hands of that facility, then, yes, they must report the typing error.

DR. JACKSON: Thank you, Jennifer.

Dr. Louis Katz will be giving the next presentation, for the America's Blood Centers.

Agenda Item: Blood Center Perspective

DR. KATZ: Things must be pretty quiet in transfusion-transmitted diseases if Dr. Katz is talking about tube shaking.

What I'm going to do, in fact, is report on a survey that we executed during November, when it was brought to our attention that this topic was going to be addressed. Dr. Davey asked me if I could talk about the blood center perspective. I'm no longer at a blood center, but recently enough, I guess, that have some competence to address the issue.

For people on the committee who don't know who America's Blood Centers is, we're a trade association. It's at last count 73 individually licensed, FDA-licensed, blood centers serving 160 million people in 45 states and also including Hema-Quebec, 2.5 million blood recipients, 3,500 hospitals, et cetera.

The red blood drops represent the fixed donation sites of America's Blood Centers. As you can see, the blue

areas are areas served by the members of America's Blood Centers. It's half the blood supply, give or take.

We do the historical antigen typings, for these three reasons. First of all, antigen-negative red cells for patients who are, in fact, already alloimmunized have a history of clinically significant alloantibodies, whether they are still detectable or not.

The second reason is to provide units for patients at risk for alloimmunization who are not yet alloimmunized. The classic example here that blood people in the audience will recognize is sickle cell disease patients. Many of our programs try to go four, five, and six minor antigens deep in order to prevent the alloimmunization that causes so much trouble in the process of chronic transfusion.

Third, and not trivial, is a reluctance both at blood centers and hospitals to incur costs, maintain staff, and incur the delays required for repeated testing of previously typed donors. So there is an operational and economic argument as well in why we do this.

The process has been described. What I'm going to describe here is essentially what we did at my former center, which I thought was more or less standard of care, and which, you will find out, is not. One or more prior donations -- in the case of my former center, Mississippi

Valley, a minimum of two separate donations -- would have been tested using licensed reagents where available, unlicensed reagents where not available, including molecular, in a variety of largely manual systems -- tube, gel. Blood bankers understand what I'm talking about. It's probably not relevant for the rest -- except that it's a largely manual process once the labeled sample is in the reference lab.

The data is archived in either the laboratory information system or the blood establishment computer system, or both -- in the case of my center, both. That data is, in fact, entered manually after the work is done at the bench. That is the case in most places. You will hear from more places as we move on.

When these units are requested or for general distribution, subsequent donations previously tested or identified, selected for the relevant negative antigens. The hospital may or may not confirm those typings, depending on their capability and the availability of antisera. In the case of my system, virtually all of our hospitals who request historically negatives, in fact, confirm them. But in point of fact, we have a substantial sickle cell program at a children's hospital, and if the recipient is not already alloimmunized, they don't confirm the antigen typings. They get their Rh- and Kell-negative

units, and if they are cross-matched-compatible, they are transfused.

This topic -- the FDA probably can’t say it, but I submitted a variance, I can’t remember if it was a year or two years ago -- time flies when you’re having fun -- because, as we and the FDA have read CFR, if we integrally label that unit -- that is, either on the base label or an attached tie tag -- we’re in violation because we have not tested on the current donation. These are the citations. The important part, I think, is in red. It’s interesting that 640.5 talks about serologic tests for syphilis, ABO blood group, RhD, and tests for communicable diseases and doesn’t mention antigens, other than ABO.

I thought that that was a nice way for FDA to get around this problem, because it’s a GMP nightmare for us to put on an antigen typing sheet all this information, put it in a shipping container with the units, and have it not attached to the unit. The opportunities for mixing it up one for the other, et cetera, et cetera, are obviously substantial. So we thought this was a GMP -- just do it. Get a variance so that we’re attaching a unit’s results to the unit.

It turns out it wasn’t that simple, or we wouldn’t all be here. So it became not that simple because there are interpretations at FDA that say that what we’re

doing is in violation of the citations I gave you from CFR, which I hope are the right citations, and if they're not, Judy Ciaraldi will tell me so.

Rick asked me at the end of October if I would talk about the blood center position. I said, yes, but I don't know what the blood center position is. I was new in my job at ABC, having just left the blood center and moved my office to Washington. So we did a survey, which we have evaluated over the last week or two. It's a very new data. We need more. That's all I will say about the quality of the data. We do need more. But we were in a hurry to be able to help deal with some of these questions.

The primary question that we want to know about is, do you do this? Do you distribute units with historical antigen typings -- that is, antigen typings not on the current donations?

The number of centers has already changed. It should have been 53 from 73, so a 72 percent response rate, which is really quite good, representing three-quarters of the 2011 collections by the ABC members. We think it's representative of practice amongst the independents.

These centers range from centers that collect 10,000 whole bloods a year up to Blood Systems, for example, that I think is at or a little bit beyond 1 million. So it's a very broad range of center sizes,

geography, sophistication, et cetera, all licensed and currently in good standing, is my understanding with FDA.

The answer was, 56.6 percent of respondents said, yes, we do, and 43 said no, which surprised me. Under current pressures from our hospitals, certainly the concept of not providing historically antigen-negative units in my system is not an option. Our hospitals would not be happy if we said, no, we're not going to do that anymore. So I was substantially surprised that as many as 43 percent don't do this.

It doesn't correlate with size. I'm not going to spend much time with this. Those that do, those that don't span the entire range of organization sizes within ABC. You will hear from the American Red Cross during the open public hearing. That's mostly the other half of the blood supply.

How many results are required -- that is, independent test results? As you can see, 63 percent require a single result, which surprised me. We require a single result on two separate donations, a minimum of a single result on two. I would have thought that that was kind of the way it is. But it's not really the way it is. You can see that a third require two separate results.

How many donations? These track exactly. There may be a flaw in the question. The bottom line is that

there are a substantial number of blood centers that require a single result on a single donation in order to subsequently call a unit historically negative.

The minimum testing -- this is kind of a mess. There are two nonrespondents. Twenty percent would accept either licensed or unlicensed serology, 27 percent licensed serological reagents only used, and 46.7 would use molecular, verified with licensed or unlicensed serology where available.

I can tell you, in my center we have no serologic reagents. If they have been typed twice with a molecular system, we would accept that unit and send it to the hospital as historically negative.

So it’s not as simple as what you see here, but it’s a pretty close flavor for what’s going on in the independent blood centers.

Here’s the method. It’s my understanding that we would get a 483 citation if we did what 60 percent of our member centers are doing, which is integrally labeling the unit -- that is, putting a tie tag on the unit. I’ll show you a picture of how that looks a little later on.

Although ISBT-128, the labeling convention that Jennifer showed you, has the capability to print these codes on the label, there’s nobody -- because of all this controversy, I would presume, in part -- nobody is doing

that in the United States that we're aware of for historical antigen typings.

This is actually how we do it -- not "we," my former blood center at Mississippi Valley. I work for somebody else now. For the uninitiated, that's a unit of blood. This is our antigen typing sheet. It's in a Ziploc bag. It goes in the shipping container, not attached to the unit. That's how we do it, because our quality people said, you're going to go to jail, Dr. Katz, if you attach that to the unit. And I don't want to go to jail, at least not for that.

Other people will do it this way. I made this one up, because we don't do it this way. I have handwritten a whole bunch of stuff on a unit. That's a tie tag. As you can see, it's not attached to the unit. That's also in a Ziploc bag, and then you have the unit which is sitting on top of the bag. These are not integral, but they are identified because there's an ISBT code here and an ISBT code on the bag, and they get matched up when they get to the transfusion service, you hope.

This is what we want to do. We just want to attach it with that rubber band so that it can't become separated during storage and inventory management and all that. We just want to attach it.

It is true that we're going to supply this

information to our hospitals. The real immediate question for us is, integral or not integral?

How many units are released as historically antigen-negative? We only got 23 responses here. Apparently people are having trouble counting. As you can see, it depends on where you are. In some places not very often is it done, all the way out to as many as 40,000 a year. That 40,000 represents -- it’s in our computer and we provide that information to our hospitals so they don't have to call us and say, we need Kell, E, Duffy A-negative units. They can look and see if we have already sent them that unit in their inventory. Other places only do it on request, and they would cluster down here.

Does that make sense to anybody? The 40,000, 35,000 out on the right-hand side represent the blood center doing a service to their hospitals to prevent one phone call back to the blood center, or one search of the database, if the transfusion service has access to the blood center’s database.

This is false negatives in the past five years. We got 30 reports here from our centers. We just asked them, how many false negatives -- that is, I said it was Kell-negative and they typed it Kell-positive or had a positive cross-match and sent it back to us and we found it was Kell-positive? That would be an example of that. So

the false negatives are the important ones. If it’s false positives, you don't distribute it as negative, so it really clinically -- it is a quality issue, but it’s not a clinical issue.

You can see quite a range here in the number of times this happened, from it doesn’t happen -- that would be my center, or perhaps Connie Westhoff’s center, New York Blood Center; we’re really good -- out to here, where they had 30, and it wasn’t the biggest center in ABC. But in response to that -- most of these 30, for example, occurred during the first two years of that five-year interval -- they revamped their procedures and have had three in the last two years. So it’s not something that gets ignored.

The 10- and 20-episode centers accept antigen-screening results from their hospitals, archive that data, and use those results, in addition to their own, for determining historically negative. That is not a practice that I was aware of. I think it's a practice that our working group needs to discuss with regards to under what circumstances you accept the results from somebody outside your laboratory.

Here are some rates. This is for Matt. He and I were talking about rates earlier today. You’ve got to have rates. We’re looking at percents here, in two formats -- units released and antigens released. Probably the most

important is units released. A fraction of a percent across almost 150,000. Twenty-three centers reported their units released with a false-negative antigen. They was a total of 89. It’s 99.4 percent compliance, it appears, despite the variability of practice that we see.

Actually, as I got into the variability in this data, I thought it might end up being worse than that, but it wasn’t. So we’re mostly getting it right, over 99 percent of the time, a little higher rate if you look at antigens, because many of these units are typed for more than one antigen and there would be a mistake only on one.

Any questions about this?

(No response)

Our experience -- we’re just a stinking little blood center out in the middle of nowhere in eastern Iowa. We distribute about 200,000 red cells a year, so we’re not really -- we’re a stinking medium-size blood center. We do distribute, and have for many years, historically negative units. We use licensed and unlicensed antisera and genotyping. We get the answer that we need to get to support the patient. The hierarchy is, if you have licensed materials, that’s what you shall use, but if you don't, you will use unlicensed reagents, including molecular methods -- in our case, the BioArray GeneChip system. Unlicensed results are flagged as having been done

with unlicensed reagents. Genotypes are not used without serologic, quote/unquote, confirmation, unless they are because we don't have antisera.

It’s practice of medicine. The point I’m trying to make is that we’re practicing medicine, and it’s substantially different than the manufacturing production-level testing that we do in our infectious diseases laboratories of when we do ABO RhD screening on highly automated platforms in a production mode.

Our results go on sort of a packing slip. They are not attached to the unit. We do not require -- because we cannot require -- that the hospital confirm our results. Our contract doesn’t allow us to tell them how to do their business in the hospital transfusion service. I think that would be an interesting negotiation to enter into at this late date in our history of relationships with our hospitals.

The practice of confirming is nearly universal, excluding some prophylactically supplied units, but not completely universal, because there are rare antisera that the hospitals just don't have.

We distributed 1,530 units with historical negative results during the past 12 months. We have had zero false negatives in five years. And our hospitals would tell us. I promise our hospitals would tell us,

right after they ask for a credit.

This is data that I think Connie Westhoff from the New York Blood Center will go into in more detail. It’s a much larger laboratory. I just want you to pay attention to the lower right-hand corner: 126,000 antigen typings subjected to confirmation. I believe this was a three-year period of time. They had, in fact, two sort of false-negative results, but only one that it would call false negative. The one was a little e false negative that was discrepant with varying reagents. That is one of the hazards of doing immunohematology. An anti-e from company A might react differently than an anti-e from company B. They are not the same reagent.

There was one M false negative that appears to have been a transcription error, a mistake in the reference lab that one would hope would be avoidable, but is not. You’ll hear more about this work a little later.

The remaining five of seven, in fact, had to do with variable antigen expression that is variably detected by variable reagents. And this is tube shaking. This isn’t PCR anymore. This isn’t a highly validated enzyme immunoassay that we use for infectious disease screening.

This is the conclusion -- and I’m going to skip this, because I think Connie will probably revisit this conclusion -- basically saying that you shouldn’t have to

retype after you know.

Now let’s define when it is that you know. In the case of the New York Blood Center, in the case of my blood center, it’s twice on separate donations. That is not uniform around the country.

Conclusions, then:

• This practice of medicine is widespread.

• Labeling regulations, as interpreted both by my quality department at my old center and by FDA, do not conform with current good manufacturing practices. Putting critical clinical information on a piece of paper separate from the unit is not, in my mind, compliant with CGMP.

• There is considerable variability of practices at ABC blood centers. I was surprised by the level of variability. That’s going to be a topic of a lot of discussion.

This has to do with the number of donations, number of typings required, how we use unlicensed reagents, whether you do or don't, and under what circumstances, accept transfusion service results or somebody else’s results, confirmation or not at the hospital, and then the labeling conventions that I have described.

Here’s our wish list. One is immediate. This was the thing that I thought was going to be a quick fix. We would just say it’s silly to have the result here and

the unit here. We think that FDA has been very cooperative in discussing routes to get GMP-compliant labeling. We hope that this meeting might move that forward. Since we're going to provide the information to the hospitals, we have to provide the information to the hospitals, why not do it the right way?

The ongoing thing is all that variability that I talked about. We have an AABB workgroup. It seems to me ideal that we would refine the data that's available regarding the variability of practice and eventually promulgate AABB standards that would address the issue of what constitutes an appropriately historically typed red cell unit and all the other things that you can see here.

What are the circumstances that require confirmation at the transfusion service? None? Can you use an electronic cross-match, which we know is occurring with some prophylactically provided units? If they have an antibody or a history of antibody, electronic cross-match is not an option. They have to do a serologic cross-match. How good is that? What if the antibody has fallen to levels that are missed in a serologic cross-match or repeat screening at the hospital?

We need to come to consensus and agreement about best medical practice in that setting and some clarity on the use of outside results.

Thanks to Ruth Sylvester, Toni Mattoch at ABC, Connie from New York Blood Center, and the ABC respondents.

I can take questions. If there are none, I can go back to my seat.

DR. JACKSON: Are there questions for Dr. Katz?

Do you know what percent of units collected have been historically typed?

DR. KATZ: It depends on where you are. I know that there's a center somewhere in Ohio where most of their units have had some level of phenotyping. At my center it's less than half and more than a quarter.

DR. JACKSON: But if you had a lot of first-time donors, you wouldn't --

DR. KATZ: Yes. Seventeen, 20 percent of any blood center's supply is first-time donors, and they are excluded.

But I would guess at my center we have at least some of this information on somewhere between a quarter and a half of donors. Forty percent is probably accurate.

DR. SIMON: Wouldn't it be just group O? Are you now doing the others?

DR. KATZ: Yes, we do. Group O red cells are at a premium, for a wide variety of reasons having to do with massive transfusion protocols and this and that and the other thing. We start with Group Os when we're looking for

something that is going to be hard, but we have a lot of data -- a database that’s approaching 10,000 donors with molecular results.

DR. EPSTEIN: I just want to provide a few clarifications about the regulatory framework. We’re not actually here to discuss the regulatory framework so much as what standards should be applied.

The first is to distinguish labeling in general from the container label. Putting anything on a tie tag is labeling. Providing an accompanying sheet, that’s labeling. Putting linked information in a database of any sort, that’s labeling. All of that is labeling.

The regulations are highly restrictive about what can do on the container label. That’s the thing that gets stuck onto the bag. That’s the container label.

I want to distinguish that there are really two questions hanging in the air. The first is, at what point can you use historical information in labeling? What that means is tie tags, databases, additional sheets, whatever. The question there for the FDA is twofold. First, what standards should there be for acquiring that information which is transmitted? The second is, at what point could you use it on a tie tag?

FDA has not taken the position prima facie that it’s violative to put historic information on the tie tag.

In fact, we don't have a position yet. It comes down to the interpretation of CFR 606.121(j). Is the listing of things that can be put on a tie tag intended to be restrictive or permissive?

We haven’t declared that it’s violative to put historic information on a tie tag. I’m sure someone will bring up instances where that has been allowed in different contexts, just not previously for cellular antigens.

So the first question about information that can be conveyed as labeling is whether FDA should step into the arena and establish standards. For example, can you tie-tag if it has been in-house testing with nonlicensed reagents? Can you provide an accompanying sheet if it has been done with licensed reagents, but it has only been done times one?

There’s a separable issue about standards for the information that can be put into labeling. That question is short of the question of what can go on the container label. Very clearly, we don't allow historic information on the container label at this point in time, because the regs say you can’t do that.

So the second-tier question is, are the thresholds for providing labeling information any different than the threshold that FDA should allow to allow actual labeling of the container with historic information.

That’s that lower right-hand quadrant that Jennifer Jones showed you, which contains additional information on the unit and already legally can contain phenotypic information if done on the current collection.

So there are these questions. I hope it helps the committee to understand that there’s a general question about labeling. That is, what standards should we apply for acquiring that information, validating that information, and providing that information? I just wish to take off the table whether it’s violative or not to put that on the tie tag, because we don't actually have a policy, and maybe that in and of itself isn’t violative, but it still might require establishment of standards.

Separable from that is the question, at what point should FDA be advised to consider allowing it on the container label itself? Which basically has the implication that nobody is going to have an incentive to repeat it. You are sort of saying that’s definitive when you put it on the container label. That’s the whole idea of the container label, that it’s authoritative.

Those are just clarifications that I hope help the committee. If not, I’m happy to repeat myself.

DR. KATZ: A couple of things in response, Jay. It’s my understanding that blood centers have been cited for using tie tags with historical antigen labeling.

That’s one piece. It’s a smaller piece than it appears, if I’m hearing you correctly.

The other is, you used the word “standards” a number of times. Standards mean one thing to a blood bank, a member of AABB, and regulations or guidance mean something else. Talk to me -- we need to know what you mean when you say standards. I think I do, but we need to be clear.

DR. EPSTEIN: We issue guidance as a statement by FDA, a way to comply with established statutes and regulations. Is this a GMP issue? Perhaps it is. Standards are not always directly enforceable, because they must be linked to underlying regulations and guidance. I think the way to think of it right now would be, what are FDA’s expectations with regard to current practice?

We can talk later about whether those are “shoulds” or “musts,” which is the distinction you’re getting at -- “should” if we recommend it and it’s not in and of itself enforceable, “must” if we think that it is the unique interpretation of a reg or a standard, and therefore it is directly enforceable.

As you know, if it becomes common practice, whether or not it was established in regs, then it becomes enforceable under GMP. And even apart from all of that, if you are a licensed establishment, we review your SOPs, and

we are either going to accept it or we're not. So de facto we establish standards when we review SOPs.

That's all a sidebar.

I guess the issue, then, is that blood establishments want to put the historic information on the container, and we're trying to figure out under what conditions FDA should permit that, through whatever regulatory mechanism.

DR. KUEHNERT: I think I'll save my questions for Jay until later. But for Dr. Katz, there was a question to the committee about whether our responses would vary if there were serologic or molecular testing performed. I just wonder if you have any comment about any differences in approach or viewpoint when comparing those two methods.

DR. KATZ: We have used a lot of molecular, over a period of several years, to be able, for example, to screen all our black and Asian donors and have a data set that tells us where to go look for what we're looking for, which we then confirm with antisera. It's very rare that we don't have any antisera, licensed or unlicensed.

The discrepancies that have come up -- generally, molecular ends up winning. We send it off to our manufacturer and they work on it and they find a new SNP, a new single-nucleotide polymorphism, that hadn't been described before. I think the molecular platforms are very

robust, but they are not yet FDA-approved, and there are a lot of good reasons why they are not FDA-approved. I think they are being held to a higher standard than hemagglutination. It’s 2012. Maybe that’s not inappropriate. They are much less subjective endpoints.

So I think they both perform remarkably well. My personal opinion -- and you will hear from somebody that has done more than we have -- is that molecular for the 33 things that we’re looking for now is probably more accurate. It has to be proven before they will be licensed.

DR. DIMICHELE: My question I could ask you, Louis, or I could ask the FDA. I understand that molecular reagents are not yet licensed. Are there plans or is that in the process? Is that something that we see as eventual? I was struck by the fact that almost 50 percent of the requirements in your survey were that there was genotyping and serological confirmation in order to -- that’s what they would use for historical labeling.

DR. KATZ: I’m sure the FDA is not allowed -- if there’s been a submission, they can’t say anything. The people that we work swear to God that they are going to get this to licensure. They’re working on it very hard. It's a very complicated process to bring these array-based methods to licensure.

DR. DIMICHELE: My second question is, as we're being asked to look at this, are we being asked to look at this independently from the requirement of the transfusion center with respect to what their obligations would be with historical typing? In other words, does this really just have to do with the labeling or does it incorporate any enforceable practice at the level of the transfusion center?

DR. EPSTEIN: I think the crux of the issue there is whether there's a responsibility to confirm the phenotype on the current unit. That may or may not have been done by the collector. The collector might have provided historical phenotyping information with the unit, one way or another, and then there's an open question whether we should require that there is confirmation. If it wasn't done by the collecting center, that burden would then fall on the transfusion service, which we do regulate.

DR. DIMICHELE: So I guess my question would be, for instance, if we said the requirements for labeling would be such-and-such, but in the circumstances of individuals who had antibodies, not only is the typical cross-match required, but labeling should be confirmed if it hadn't been confirmed by the center on that donation, just because of the potential for low-titer antibody recipient -- something like that. Can we --

DR. EPSTEIN: That’s at issue, yes.

DR. DIMICHELE: Okay. So we should be taking all of that into consideration.

DR. EPSTEIN: Yes. Again, one of the key questions -- and I think it is in the questions for the committee -- is, should the historic antigenic phenotype be confirmed on the current collection? If the answer is yes, then that burden might fall on the collector or it might fall on the transfusion service.

DR. DIMICHELE: But it might be also situation-dependent.

DR. EPSTEIN: Yes, but the general situation is that the patient either has a known antibody or historic antibody. That’s why you are looking for antigen-negative units. So I’m not sure what the exception is. That is the general situation.

DR. JACKSON: Our next speaker is Dr. Lynne Uhl, from Beth Deaconess Medical Center, who will give a transfusion service perspective on the use of antigen-typed red cells.

Agenda Item: Transfusion Service Perspective

DR. UHL: Thank you, and thank you to the members of the committee for inviting me to speak this afternoon. As said, I’m giving the transfusion service perspective.

Just to point out to everyone, I have no

disclosures. It was discussed earlier today, but I just want to put it out in front of everyone.

What I am going to do during this session is present three clinical cases that are cases from the transfusion service that my colleagues and I were actively involved with.

The first is a 67-year-old female with psoriasis secondary to autoimmune hepatitis, found to have an anti-Duffy A and anti-E on routine blood bank workup during her pre-transplant evaluation. The way we manage these is to evaluate the patient and develop a clinical consult that's issued to the physicians. Bottom line of our consult was that we alerted the liver transplant team to the fact that antigen-compatible blood is not readily available and that, in fact, in this particular instance 15 percent of donors would be negative for both antigens combined.

We're compelled to do this. As many of the clinicians in the audience know, these patients can present at any time with an upper GI bleed that we have to manage, and also the anticipation of the upcoming surgery.

In terms of transfusion management of our liver transplant patients, we typically will cross-match, in advance of the surgery when we know that they have been called in for a transplant, 15 to 20 antigen-negative units. We will issue 10 to 15 units to the OR at the

beginning of the surgery. Once these units have been transfused -- and we are in close communication with the liver transplant team during the height of surgery -- we will move to antigen-untested units and issue on electronic cross-match, in fact. We take the antibody out of the patient's header. Then we reinstitute issuance of antigen-negative units upon completion of the surgical procedure.

The thought behind this is that if a patient is briskly bleeding and being fully replaced with red cells, plasma, and platelets, the antibody has been diluted out and will be of probably less clinical significance than the blood transfusion support the patient requires.

Clinical case number is a 35-year-old G3P1 at 20 weeks gestation, who was referred into our institution with a history of an anti-Kell, with a titer of 2048 -- pretty high -- and an anti-JK^a. She was seen by our high-risk maternal and fetal medicine for a PUBS procedure, periumbilical blood sampling, with the intention, if necessary, for intrauterine transfusion. As with our liver group, we apprise our obstetricians that approximately 20 percent of the donor units would be antigen-compatible

In terms of our management of patients like this, we do use liquid units that are less than 14 days of age, hemoglobin S-negative, leukoreduced and irradiated, and negative only for the offending antigen -- in this case,

for intrauterine transfusion.

Finally, case 3: This is a 75-year-old male transferred from a rehab facility with cardiogenic shock. The team requested four units of emergency-release blood. Notable in this particular case was that this patient had recently undergone an aortic valve replacement two weeks prior at our institution. During that surgical procedure, which was more complicated than the run-of-the-mill surgical procedure for this admission, he received 10 units of packed red blood cells. At the time his antibody screen was negative, but when he re-presented in cardiogenic shock, he now had a positive antibody screen for Kidd-A antibody. We had no screened units in inventory.

As discussed earlier this morning by Jennifer, with respect to clinical use of antigen-negative units, they are indicated in patients with alloantibodies. This is in accordance with the AABB standard 5.14.2.1. We are required to use antigen-negative units in patients who have clinically detectable alloantibodies or historically detectable alloantibodies. Those red cell units need to be serologically cross-match-compatible.

As many of you in the audience know, about 3 percent of transfused patients will form alloantibodies. But it really is a much more complicated picture. In fact, alloimmunization rates are notably higher in subsets of

patients. Possible reasons for this include antigen disparity between the donor and the recipient, variable antigenicity of red cell antigens, and there has been a hint in the literature of perhaps a threshold effect, so the more a patient is transfused, the higher risk there is for alloimmunization.

This has led to, as someone discussed earlier, the consideration for prophylactic antigen matching in patients with hemoglobinopathies, in particular sickle cell disease. The thought is that this reduces the rates of alloimmunization and also, with prophylactic antigen matching, prevents delay in getting units to patients that may be impacted in a negative way if the patient forms a new alloantibody.

This is data that I want to share with you that was recently discussed by Dr. Fasano at our AABB meeting. In a nutshell, what it shows you is that there has been variability of practice over the years with respect to matching algorithms in patients with sickle cell disease. What you can see early on in these studies reported on situations where patients were matched only for ABO and RhD, and they experienced a very high alloimmunization rate. In terms of risk per 100 units transfused, you can see that it ranges anywhere from a low of 1.7 to a max of 3.8 in this particular publication.

However, when limited antigen or extended antigen matching is employed -- and by limited, I mean matching for the Rh and Kell system, extended matching, as you can see, as highlighted in the footnote here, including additional antigen systems -- the rate, as well as risk per 100 units, is dramatically lower.

This led to a recent survey among US academic centers that was recently published in *Immunohematology* to look at exactly what folks are doing, particularly in pediatric centers which manage patients with sickle cell disease. As you can see, there is still a slight variability. For example, Johns Hopkins primarily will match their patients for ABO and RhD until a patient forms a new alloantibody, at which they will jump to extended matching. Other centers use initially a limited antigen matching for transfusions, again moving to more extensive antigen matching, particularly in this case, once alloantibodies are formed. Three of these sites will move to limited plus the antigen once an alloantibody is formed.

In all cases there appears to be a combination of patient and donor testing by molecular techniques in order to better match both the patient and the donor.

Other clinical uses include patients with panreactive autoantibodies. This is a publication from Shirey et al. back in 2002, in which these investigators

with a blood bank endorsed extended prophylactic antigen matching for patients who presented with panreactive antibodies. They go on to say in this publication that it did reduce the risk for further alloimmunization in their patient population and also expedites pre-transfusion serologic testing. Specifically, this means that if they have fully matched the patient, they can continue to provide antigen-matched components without having to do the additional serologic steps at the bench -- specifically, autoabsorption or heterologous absorption, depending on the patient’s transfusion history.

Another use of antigen-negative units is in women of childbearing age, specifically prophylactic antigen matching for select antigens. In fact, the UK endorses the use of issuing women of childbearing potential Kell-negative units to prevent sensitization, unless there is urgency of request which precludes the provision of such units.

The Netherlands, another country that endorses the use of prophylactic antigen matching, actually extends to include both girls and women of childbearing age and also extends to both the E and C antigen, if the female is negative for those particular antigens, again to prevent sensitization and the downstream consequences of hemolytic disease of the fetus if a mom becomes alloimmunized.

I didn’t realize I would have so many blood bankers in the audience, but just a quick primer.

Certainly our biggest clinical concern for alloantibodies is acute immune hemolysis. Far and away, ABO immune hemolysis is the most severe. The reason for this, as many of you know, is that we all have preformed IgM antibodies that are present in very high titer. These IgM antibodies are very facile with fixing complement on the surface of the red cell.

In contrast, non-ABO antibodies can cause less severe hemolysis, but it’s not to say that you won’t see clinically significant hemolytic transfusion reactions. The reasons for this are that the antibodies are primarily IgG in nature and are directed against the protein antigens on the red cell surface. They also require previous red cell exposure, either through maternal-fetal blood exchange or through prior transfusion. Many of these antibodies do not fix complement, and as a result, you don't see the brisk intravascular hemolysis. Rather, it’s extravascular.

I have included two cartoons of what I call the pathophysiology. This is of intravascular hemolysis. As depicted here, the red cell is sensitized or coated by the antibody interacting with the antigen, IgM in this case. There’s also IgG. That goes on to activate the complement system, culminating in the formation of the membrane attack

complex that actually pokes holes in the red cell membrane and results in red cell lysis.

In contrast, extravascular destruction takes a different path. Again here the red cell and antibody are interacting at the level of the antigen. This antibody-antigen complex interacts with Fc receptors on the reticuloendothelial cells and actually can then take one of three routes: The red cell can be entirely ingested by the cell. A portion of the membrane can be pinched off that contains the antibody-antigen, resulting in spherocyte formation, which is a common hallmark on peripheral smear of a red cell transfusion reaction. Then finally, in some cases, this antibody-antigen interaction with the Fc receptor can cause direct cell lysis.

Hemolytic transfusion reactions certainly carry some morbidity, but they also carry a risk of mortality. This is FDA data pulled together as published in Vamvakas's book on decision making in transfusion medicine, data from 2005 through 2010. What you can see is that about 25 percent of the reports of fatality to the FDA during this period were the result of hemolytic transfusion reactions. The actual number is that there were 75 cases reported to the FDA during this period of time.

Bringing it closer to home, I am giving you pretty much a personal perspective from our hospital. We

are a tertiary academic medical center. In terms of stats and facts, we're a modest to larger-size hospital facility, with 649 beds, 430 med/surg, 77 ICU, and 60 Ob-Gyn beds. We are a level 1 trauma center, so we have those helicopters flying in pretty much on a daily basis. We also have a level 3 newborn nursery care, again attesting to the level of acuity of our institution. We have about 5,000 births per year and 41,000 inpatient discharges and 57,000 ED visits a year.

In terms of our transfusion activity, this is captured as calendar year for the last three years. You can see that we transfuse about 19,000 red cells annually. When you look more closely at transfusion activity by service, in terms of the red cells, we're about split 50-50 in terms of red cells going to medicine service patients and surgical patients. I'll just also point out here that as far as our platelet transfusion, the bulk of our platelets go to our hem/onc patient population, but we're not talking about that today.

In terms of use of antigen-negative units, certainly we use them for alloimmunized patients, for routine transfusion, in support of our alloimmunized liver transplant patients, and management of moms, babies experiencing hemolytic disease, fetus and newborn.

We also employ prophylactic antigen matching for

sickle cell. We employ the limited antigen matching, Rh and Kell. We also provide Kell-negative units to patients that are admitted to our obstetrical service, and we also provide limited antigen matching for Rh and Kell in patients with warm autoantibodies that are detected by solid-phase PEG and LISS tube testing. So they are broadly reactive.

In terms of antigen-negative units that we received from our blood supplier over the last year and a half -- so this is January 2011 through September 2012 -- we inventoried a total of 1,057 units. When I was looking at this data, I was struck by the fact that the largest number of units was actually negative for two antigens and then that was followed by three antigens. But interestingly, we inventoried 84 units that were negative for four antigens and 38 for six antigens -- just speaking again to the complexity of patients at our institution.

We are a site that receives red cells from one blood supplier. I have taken a picture here of the units as they come into us. Similar to Dr. Katz, I learned a lot in getting ready for this talk about how units are handled. In fact, in our case we receive units where the component itself has been tested. We do not inventory historically labeled units, because that’s what our blood supplier supplies to us. As you can see, this unit has its tie tag

integrally connected by a tight string.

On what I call higher power, based on my pathology background, this is the tie tag that is affixed to the unit and specifically labeled negative for E, Kell, S, Jk^b and Cw. We may have only requested E- and Kell-negative units for a particular patient, but this unit came in with all of these antigens labeled as having been tested and negative. As you can see, there’s also an area here where our blood supplier can indicate to us that they have tested a particular unit with an unlicensed reagent.

What we then do with these units is enter them into our computer system from the tag tie. This is a manual test entry into our system. We reserve it to the patient. Then we will release them to our general inventory once the acute needs for the particular patient are no longer present, and so they are available to us in our inventory when the next patient comes in with specific requirements.

We also do laboratory-based antigen typing. We routinely perform antigen typings for common antigens. We have antisera for Kell-Cellano, Rh, the Kidd system, the Duffy system, and MNSs system.

What I was surprised to find -- from the transfusion physician perspective, I assumed that most of our antigen typing related to the patient testing, because

we see patients with antibodies all the time and want to confirm. But, in fact, I was informed that we use the majority of our antisera for screening for antigen-negative units that are sitting on our shelves, to meet our patients' needs.

The expenditure on antisera is about 11 percent of our reagent budget, so it's not pennies by any means. In total, it comprises about $53,000. This is the reagent budget. This doesn't include the blood part of our budget.

I'm not going to leave you hanging. I will tell you what happened with our liver patient, if you recall, Duffy A and anti-E. Transplant surgery was indeed successful. We engaged our blood supplier to alert them that this patient was in the wings, and our blood supplier screened their inventory and at the ready had units available until that patient was called in for surgery. It was a constant dialogue back and forth to make sure that we had units available. Of course, when they delivered the blood, they knew the patient was going into surgery and there was no longer a need to keep a unit set aside.

This patient received nine units of red cells, all antigen-negative, 14 plasma, six apheresis platelets, and one dose of cryo.

As far as our obstetrical patient, this patient underwent 11 PUBS procedures with accompanying intrauterine

transfusion of Kell and Jk^a antigen-negative red cells. I'm pleased to say that it resulted in the delivery of a live-born female at 34 weeks gestation. At delivery this baby had a hemoglobin of 9 grams per deciliter and immediately underwent a two-volume exchange transfusion, of course, with antigen-negative units that we had brought in from our blood supplier. The baby was discharged to the community hospital at day 15.

In terms of our cardiac patient, our resident got involved with the thoracic fellow and alerted him of the positive antibody screen, and so the ER-release blood was not transfused. We immediately called our blood supplier to request six units of A-negative, Jk^a-negative red cells. They arrived within two hours of making that phone call. We also at the same time immediately screened the emergency-released units and found that one of the four units released was, in fact, Jk^a-negative, and this unit was transfused. The others were returned to the blood bank.

The patient is alive and well.

In terms of considerations regarding antigen-negative units, as I have described, we are using them to manage patients with alloantibodies, as well as provide phenotypically matched red cells to unique patient populations, such as our OBS population, to prevent alloimmunization. We also use them to ease the burden of

serologic evaluation of complex patients -- for example, our warm auto patients.

Our current practice relies heavily on the blood supplier to provide our transfusion service antigen-negative units. That’s certainly okay in cases where red cell transfusion is planned. We can have a dialogue. It also, in point of fact, optimizes inventory management. But it can be problematic, as in case number 3, where red cells are urgently needed for transfusion. The point is that if we had the information, based on solid historical typing, we could go to our blood refrigerator and find units for transfusion much more readily.

It goes without saying that we have limited technical resources for inventory screening. Basically on nights and evenings, we have maybe two FTEs in our blood bank. There could be bad cases going on in the OR at that time. It does pull someone away to have to go and physically screen those units with reagents. But we do manage to do it.

In terms of future considerations, in light of the dialogue, labeling of units based on historical phenotype or molecular type offers opportunity, in my view -- and I think for many of my transfusion medicine colleagues -- for enhanced delivery of appropriate red cells to patients in time of urgent need. It also offers

the opportunity to reduce duplicative testing, both on the blood center side and the transfusion medicine service side. That can reduce cost of overall inventory management.

In terms of enhancing the acceptability -- and I think we have started that conversation here today -- these following points are things that I would like to bring forward to you. Personally, and again polling colleagues -- certainly not in a definitive survey format -- the consideration for testing being performed on two separate donations would enhance the acceptability. It goes without saying that using validated methods -- unlicensed methodology, certainly if it’s validated, is not inappropriate.

I think, too, what we have started hearing is that there needs to be in place a robust process to connect that donor historical type with the current component that is being collected and then subsequently issued to the transfusion service. Whatever supports can be put in place to help shore up the system would be greatly valued.

I would also emphasize the importance of using ISBT labeling format to capture antigen typing information. As you could see, our current process at our institution is to manually transcribe from that tie tag into our computer system. That can pose issues.

That’s all I have to say this afternoon. Thank you for your attention.

DR. JACKSON: Thank you, Dr. Uhl.

We have time for one or two questions before we take a break.

DR. DIMICHELE: Two quick clarification questions. Given that all of your units are actually typed on that donation, if I understand you correctly, you do not --

DR. UHL: I skipped over that. Our site does not retest when it comes in. In fact, in a back-of-the-envelope poll, that’s pretty uniform at the transfusion services. It was about ten transfusion services that I queried, and that’s the practice that is in place.

DR. DIMICHELE: And what percentage of your typed units are used for prophylactic transfusion versus alloimmune patients?

DR. DIMICHELE: It’s hard. We do not have a big sickle cell population. We have a fair number of our warm autoantibody patients. But I think, far and away, our antigen-negative units go to patients with known alloantibodies, either currently demonstrated or historical.

I’m sorry, I’m not a good one with giving out numbers.

DR. STOWELL: Just to follow up on her clarification question, Lynne, the places that you talked to that didn’t do their own type confirmations, were they receiving units which had been typed on that particular donation?

DR. UHL: On that particular donation, not historical, yes.

DR. PIPE: In those situations is there some reason why the integral label of the unit is not relabeled, if the actual unit has been tested for all those antigens? You showed the tie tag, but is there any reason why the actual integral label is not changed when it has been tested?

DR. UHL: I don't know the answer to that. We have one blood supplier. They are represented here, and they may be able to answer that question. But we have always received it as a tie tag.

DR. PIPE: Even on the current donation?

DR. UHL: Yes.

DR. KATZ: I believe they don't use 128 labeling yet.

DR. JACKSON: Any other questions from the committee? Dr. Katz?

DR. KATZ: How far is your blood supplier from your hospital?

DR. UHL: Probably 20 miles as the crow flies. Depending on traffic, it can take anywhere from four hours to 20 minutes to get to our place. We’re close. We are fortunate in that respect.

DR. KATZ: For the uninitiated -- actually, most of the people on the committee are initiated -- for example, my center serves 80-some hospitals in four states. We can be as far away, even with no traffic -- which is not infrequent in Iowa, actually, if there’s a road -- we can be five or six hours away if we get an urgent request for antigen-negative units.

DR. JACKSON: Thank you.

We’re going to take a 20-minute break. Why don't we come back here about 2:10.

(Brief recess)

DR. JACKSON: We’ll start again with three additional speakers who we are very fortunate to have come to share their expertise and experience. Next will be Dr. Denomme, who is the director of immunohematology and transfusion services at the Blood Center of Wisconsin. He’s going to talk about red blood cell genotyping experience in the blood bank setting.

Agenda Item: Red Blood Cell Genotyping: Experience in the Blood Bank Setting

DR. DENOMME: Thank you. Good afternoon.

I have been asked to give an overview of red cell genotyping and the published literature as it pertains to historical antigen labeling on tie tags. The reason for this request, so I understand, is that, for the most part, genotype collections are composed of historical data, and therefore it’s relevant to this afternoon’s topic.

My objectives today are to understand red blood cell antigens, immunization of those antigens. I think we have had some good discussion so far. That will be a very brief overview. I do want to define the differences between a phenotype and a genotype, with the take-home message that a genotype is a predicted phenotype. Third, I would like to review the evolution of red cell genotyping: How did it come about? Finally, I’ll review six benefits that can be realized with red blood cell genotyping.

Just by way of an overview, most of you are familiar with your blood group. Blood groups are expressed on red cells, with A, B, and O typical antigens that you would know. The Rh factor is also known as RhD. People are either Rh-positive or negative.

During the banking of blood, the ABO and Rh are tested on every unit every time. The reason for this is that there are severe consequences with transfusing the wrong unit to the wrong patient. If someone has group A red cells, they would have A antigen on their red cells and

have anti-B. It’s the presence of these natural antibodies that makes transfusions life-threatening if we don't adhere to ABO blood groups.

RhD is very immunogenic, and we have learned through the years that we should match, because upwards of 80 percent of people will make an anti-D if Rh-negative and transfused with an Rh-positive unit.

Most people don't know that there are many other blood group antigens on red cells. In fact, there are over 300. The count is 324 different red cell antigens that have been characterized to date. These are termed “minor blood group antigens,” and they are also present on red cells.

They are not actually matched during transfusion. There are just too many of them. However, humans can make antibodies to these antigens as a result of transfusion or pregnancy. You heard a figure this afternoon. Around 2 to 3 percent of the population will make an antibody to a minor blood group antigen after exposure in transfusion or history of pregnancy. However, in some chronically transfused patients, like those patients with sickle cell disease, upwards of a third of patients will develop antibodies.

Like red cell ABO antibodies, these antibodies can cause serious transfusion reactions. Therefore,

hospital labs routinely examine patients' blood for these antibodies before transfusion. If identified, the patient is given antigen-negative blood. By that we mean that the blood transfusion must lack the antigen to the antibody present in the patient's blood. In addition, prior to transfusion, a cross-match is performed. This is where we mix blood of the donor with the patient in a test tube to determine if they are compatible. In this way, we ensure that blood is compatible and safe to transfuse.

A little bit about phenotypes and phenotyping. "Phenotype" is a term used to describe what is expressed on the surface of red cells. For example, if I'm group A, my phenotype is A because I have A antigens on my red cells. Minor red cell antigens are determined with reagents that contain antibodies from human serum. There is a process to determine which antigens are expressed on red cells, and this process is called serological phenotyping.

Both FDA-licensed and unlicensed reagents are used, so long as the unlicensed reagents are shown to be compliant with FDA regulations.

There are multiple methods and a lot of different antisera. They are all based on agglutination. They are mostly performed, by and large, manually in a test tube, as I show on the right. Red cells agglutinate, and it's easily visible with the naked eye. We know that there is a

limited supply of some of these reagents.

What is the blood center’s role in finding antigen-negative blood? The ability to find antigen-negative blood really relies on three things -- first, the frequency of an antigen. It can range from an antigen-negative blood like E-negative, as you heard earlier this afternoon, which is relatively common, to something like U-negative, which is very rare in the donor population. There are instances when multiple antibodies in a patient occur, and therefore multiple antigen-negative blood must be found. When they are negative for a number of different antigens, this can be a rare situation, in order to find that type of unit.

Another challenge is the number of units required. One patient rarely needs one unit. Therefore, the blood center must find enough blood for the patient’s needs.

Sometimes physicians, as we have heard, ask for antigen-matched blood. That term is used to mean that they want blood antigen-matched between the patient and the donor so that the patient will not make any antibodies. These are additional demands put on the system.

Third, as we know, some donors stop donating, so that particular antigen type is lost. Donations are generally random. We don't time these donations amongst

our donors. So sometimes what is sitting on the shelf is of a lower availability than what’s in demand.

I would like to review the current status of phenotyping. It’s rather labor-intensive. There are many methods, with a limited number of reagents. At times, the transfusion services are doing their own testing, as you have heard.

On the other hand, there is a limited supply of some reagents -- for example, anti-s -- and if we wanted to do some massive screening of our donors, it could put a strain on the actual national supply of a reagent.

Some specificities clearly don't exist. I think the example by Dr. Katz was Dombrock-A. Some requests are difficult to fill in a timely manner, which means things like surgery are delayed and patient care is otherwise reevaluated.

Now I will explain genotyping of red blood cells as an alternate to phenotyping. Genotyping is a testing process that evaluates the genes of red blood cell antigens. Here we combine DNA with different reagents to determine a donor’s genotype. Therefore, a genotype result is used to predict the phenotype, or what would be expressed on the red cells. By and large, the results are not complex. It’s usually a one-to-one relationship: A genotype reflects a phenotype.

It’s really important to stress that genotype information is encoded in our DNA. DNA is very easily obtained and used in the lab. It’s obtained from blood. Genotypes are inherited and do not change throughout our lifetime.

Now to put the context of genotyping in that of red blood cell antigens. The 324 red blood cell antigens have been organized by scientists into 33 blood group systems, or genes, and each of these genes is made up of nucleotides. In many instances these genes differ by one nucleotide, and these nucleotide differences are called single-nucleotide polymorphisms. It’s pronounced “snip.” I’ll use that term quite a bit. One SNP, or one nucleotide change, can equal one red blood cell antigen. Genotyping -- also called SNPing -- has been applied to donor testing to address the gaps in phenotyping.

Red blood cell genotyping has become a solution to the problems of phenotyping. Because of the current state, phenotyping probably focuses on about 18 red blood cell antigens. With genotyping, the same 18 antigens can be detected, but because we know a lot about these genes that express these antigens, we can genotype for many more antigens than we actually phenotyping. The method of SNPing can detect that single nucleotide, shown here in red, T, at a specific location in a specific gene to

indicate a specific antigen. The ability to predict many more red cell antigens among donors helps us provide antigen-negative blood to the patient who has corresponding antibodies, so that we can provide a safe transfusion.

Here's the relationship between genotype and phenotype. The minor red blood cell antigens are the result of single-nucleotide polymorphisms. Scientists have organized this genotype information into a set of rules so that we all speak the same language. For example, if I'm talking about the Rh system, and specifically the E or the e antigens, I'm looking at the RHCE gene. I'm looking at a specific change that has a specific location designated by a worldwide number. This designated change -- when a G is present, E is present, and when a C is present, e is present. This is always the rule in this case here. It can be applied to any of the minor blood group antigens that we see in transfusion medicine.

A second example of Kidd, which you heard earlier -- it works out that an A at a particular position in a particular gene designates Jk^b and G designates Jk^a.

I would like to show you how this works in the following diagram. On the left a gene is being transcribed. Through the transcription machinery, a protein is made that goes to the surface of the red cell. This is the E antigen in this example. On the right, it's

the same gene, but it’s a different copy of it, the e. There’s one nucleotide change that results in a different amino acid incorporated into the growing protein. This protein, on the surface of the red cell, looks like e, and we have antisera that can recognize e. So now we have a relationship to one nucleotide and the expression of an antigen versus its sister antigen.

Because phenotyping determines the antigen on red cells and genotyping predicts the antigen, there has been great interest in the correlation of these two approaches. The question is, do I get the same result? There have been seven international studies to date that have addressed this question. These studies range in size from 29 samples to over 3,000 samples. All of these analyses come to the same conclusion: The genotype correlates extremely well with the phenotype.

At the Blood Center of Wisconsin we were able to compare over 2,000 phenotypes with their corresponding genotypes and found two phenotyping errors attributed to a manual testing and discovered two new genotypes. In total, there was a 99.9 percent concordance between the phenotype and the genotype.

Now I would like to summarize how genotyping studies have expanded the scope of red cell antigens. Genotyping includes common antigens, which you see on the

top here, that are important in transfusion, but also identifies variant and null alleles -- by null alleles, we mean neither of corresponding antigens is expressed due to gene changes -- but also includes rare antigens and, in some instances, the RhD antigen is evaluated, and variations of RhD are also detected. For the most part, the antigens listed in green are commonly important for safe transfusions. However, the remaining antigens on this page are all important for patients who have antibodies. Genotyping appears to be the only way to find antigen-negative blood for them.

Now I would like to review what I have found to be six benefits of red cell genotyping.

This is a rather busy slide, but I'll walk you through it. This slide illustrates the most important benefit of using genotyping as a screening tool for screening blood donors. At our blood center we genotyped over 30,000 blood donors in 2010, and from that information, we were able to increase the pool of antigen-negative donors, which are confirmed by phenotyping. On the right I illustrate that from 30,000 donors, for a particular type called R1R1, we increased our donor pool by 3,000 or more, R2R2 300, and if those donors are also evaluated for other antigens, a total of six antigen-negative units, 123 out of 30,000 donors. This would be

virtually impossible to do with phenotyping.

We have been able to increase the number of donors -- these are the multiple antigen-negative donors. We have also been able to find nearly 100 rare donors, including hrB-negative, an antigen called Lu-b-negative, and Yt-a-negative. No phenotyping reagent exists for hrB.

As a result of the genotyping, we have more liquid units available at any one time. If we have screened 30,000 donors, the incidence of those donors coming back provides more liquid units that we can confirm. We also are more able to support antigen matching, not only for patients who need antigen-negative, but if we want to match the patient to the donor. Of course, with this expanded pool of donors, we are able to improve our turnaround time, and we're better able to meet patients' needs.

The bottom line is that we're able to be more flexible in what we can find and provide for our donors.

A second important benefit of genotyping is what I call a quality-assurance exercise, which has a clinical impact. You may not know, but the RhD gene occurs occasionally in Rh-negative blood donors. It's due to the weak expression that escapes FDA-licensed reagent detection. Every unit being tested every time, there are some examples of RhD that are too weak to be detected in

the routine environment.

There have been ten studies around the world looking at the frequency of RhD genes in Rh-negative donors. It ranges from very low, something like .6, to as many as 25 percent of the Rh-negative population. The important concept here is that once an RhD gene is seen in an Rh-negative donor, there’s a risk that they express this gene. Therefore, all of these studies have recommended that these donors be taken out of the Rh-negative pool to avoid potential anti-D from a transfusion.

The third and fourth benefits are the detection of weakly expressed antigens. We touched on this topic a little earlier today. Some antigens are weakly expressed, some minor blood group antigens, and we end up with a negative result using reagents, which can be an error. Red cell genotyping is not affected by the weak expression. The genetic information doesn’t change. It’s encoded to be weak, but genotyping ensures that donors are correctly identified as antigen-positive rather than missed because the expression is very weak.

The other alternative is the discovery of new genetic information. Sometimes, as we compare phenotypes and genotypes, these two results don't correlate. When a genetic investigation is performed on these discordant results, we are able to discover new genes. Once we know

about these new genes and their frequency in the population, we can improve genotyping platforms to be more accurate.

Number 5 is the detection of altered antigens. Sometimes there is a variation of the Rh-e antigen described in about 2 percent of African-American blood donors. It’s not possible to phenotype these blood donors, but in genotyping, as I showed you, at the Blood Center of Wisconsin, we identified nearly 100 donors who were hrB-negative. These are excellent donors for transfusion of patients with sickle cell disease to prevent incompatible transfusion, since 2 percent of these patients will also have this genotype. Therefore, red cell genotype matching can prevent transfusions [sic] in a setting where a phenotype cannot be performed.

Lastly, we can use genotyping in a reverse situation. We can detect the variation among red cells that are used in a blood center. Blood donors who are phenotyped are actually recruited for their blood unit to be made into reagent red cells. These reagent red cells are used by transfusion services to detect antibodies in transfused patients. Of course, since these reagent red cells come from blood donors and they are phenotyped, the genotyping, when applied to this set of donors, can uncover any antigen variation or weak antigens that may compromise

the quality of that donor and ensure that these reagents should be used in a GMP/GLP environment.

How about the use of historical genotyping data? What can we conclude?

Genotypes are inherited and do not changed throughout life. Genotyping increases the scope of antigens that can be detected.

The genotyping process must be validated. Data transfer from instrument to databases and the use of the data should be demonstrated to be of high quality. There should always be a way to determine that an antigen result was obtained by a genotype test. I believe this to be very important. But it’s not necessary to convey that information on the tie tag or the label.

Labeling blood with historical genotype data, it turns out that two historical phenotypes, two historical genotypes, or one historical phenotype and one historical genotype are all very accurate. All of the above are safe to use and label blood for transfusion when performed on determinations from, in my opinion, two separate blood donations.

Thank you very much.

DR. JACKSON: Thank you, Dr. Denomme.

At Wisconsin, do you genotype every single unit collected at the blood center?

DR. DENOMME: No. In 2010, we genotyped 30,000 of our repeat donors. We try to figure out how many donors stop donating in any given year. We do a maintenance to hold that at about 30,000 donors.

DR. JACKSON: I see.

Questions?

DR. DIMICHELE: Of the 30,000 donors, is most of your historical labeling on the basis of two historical genotypes?

DR. DENOMME: No. We have seldom done any repeat genotyping. The present form is that genotyping is a screening tool. When we find donors of interest, we phenotype them to confirm that they express phenotype. There’s a small group of antigens where we don't have reagent antibodies. Those are genotyped a second time in a different method. In a few instances, like the Dombrock, as I mentioned, we would use two historical genotypes.

DR. DIMICHELE: What is the expense burden in order to do this? Does it increase the cost of those red cells significantly? Is it a major burden on a providing center such as yours?

DR. DENOMME: We’re doing this in a diagnostic environment where we are trying to understand what the benefits would be in terms of the patient, in terms of finances. We haven’t passed on that burden to the end user

yet. We did 30,000 genotypings in 2010 for a reasonable internal cost, borne out by the phenotyped revenue. We are evaluating how that genotype information is benefiting us in less cost moving forward. So we're not really generating revenue. We're kind of limiting our costs.

One of the things that we don't screen donors anymore for is e-negative, Yta-negative. There are a number of antigens where we have unlicensed reagents. Those reagents are now frozen, because we have such a huge inventory of donors that have been genotyped that we no longer have to have a couple of people sit down and do nothing but phenotyping all day to find these donors.

DR. JACKSON: Thank you, Dr. Denomme.

Next we have Dr. Mindy Goldman, from Canadian Blood Services, who will give her talk on "Red Cell Antigen Labeling: The Canadian Experience."

Agenda Item: Canadian Experience

DR. GOLDMAN: Thank you very much. I would like to thank the FDA and the meeting organizers for inviting me.

I would like to point out that if you're looking at the paper copies of my slides, some of the labels have vanished. Hopefully the actual slides have all the slides, but the paper is missing some of the slides, for some reason.

I’m very briefly going to discuss the need for antigen-labeled units, give a brief introduction to the Canadian blood system, and I’m going to spend most of my time giving the answers to the very specific questions that I was asked by the FDA.

The need for antigen-labeled units has been very nicely covered by Lynne in her talk. In Canada, as in the US, we have an increasingly diverse patient population. There is use of prophylactic antigen matching in patient groups such as sickle cell anemia patients. A lot of those patients do have antibodies, and they are increasingly getting exchange transfusion on a regular basis, which puts a lot of pressure on the hospitals. The antisera are costly, and some of them are quite rare, so it’s hard for hospitals to stock them. There are pressures on the hospital transfusion services to rapidly supply phenotyping in the kinds of cases that Lynne described.

The Canadian system: We have two blood operators, Canadian Blood Services and Hema-Quebec. Hema-Quebec covers the province of Quebec, as you might guess from the name, and Canadian Blood Services covers the rest. We have a high rate of repeat donors and a high donation frequency -- not too good if you’re giving a talk about iron stores in donors, but pretty good when you’re giving a talk about phenotyping.

We have been on the MAK PROGESA system since 2003-2004 at Canadian Blood Services. Our inventory is managed nationally. We send inventory from one site to the other all the time. Our hospitals are not charged for phenotyped units. Actually, they are not charged for anything. Hema-Quebec has used the MAK PROGESA system since 1999. There is some sharing between Hema-Quebec and CBS, particularly for very rare units, where we help each other out.

I'm not going to discuss red cell antigen typing at CBS. This is a rather funny-looking map of Canada. You can see that up until fairly recently we were doing phenotyping in a lot of different sites. We have now consolidated down to Calgary and Toronto as the only two sites where we perform phenotyping.

These are where we have our two donor-testing laboratories. Those laboratories are the ones that are doing the TD marker testing using the PRISM. They do the nucleic acid testing, ABO, Rh, syphilis, CMV on the Olympus. They do the red cell antibody screening and antibody identification in donors. These activities are covered under our blood license, and these laboratories are inspected by Health Canada.

With consolidation to donor testing, it allowed us to completely standardize our procedures, which was

difficult to do when we were doing phenotyping in a variety of different labs all over the place, to use licensed reagents and procedures, to automate testing and the transfer of results into the PROGESA system. We feel that all these areas will reduce errors, both in performing the test and in transcription of results. It allows us to perform mass phenotyping on thousands of donors and hopefully meet the requests for phenotyped units with labeled units that are in inventory -- in other words, to reduce the need to do demand phenotyping when an order comes in where we don't have an actual unit that is already phenotyped for the hospital.

We are currently using the Galileo instrument, which is a solid-phase automated instrument, for Rh C, c, E, e, and Kell typing. We selective O-negative, A-positive, and O-positive regular donors. All these testing antisera are licensed specifically for the Galileo for those antigens. All the results transfer over into the PROGESA system, whether the donor is positive or negative for the antigen.

We then do manual tube testing for Duffy, Kidd, S, and s, with licensed reagents on units that look interesting from the Rh and Kell testing. For the manual testing, only the antigen-negative results are entered into the computer system.

Now our, hopefully, answers to the FDA questions.

The first question was around the quality of antigen typing results and what we do there. For the manual tube testing, the antisera are chosen based on performance of the reagents, the package insert meeting our GMP needs and, of course, the cost per test. We try to qualify three different vendors for each reagent. We have a primary reagent that's used in screening and then we have two other reagents that are used as a second test on first-time antigen-negative donors for manual testing, and also in case the first reagent, the primary reagent, is not available for some reason. As I mentioned, the reagents used on the Galileo are specifically licensed for solid-phase testing on that instrument.

Starting in the fall of next year, we're going to be switching to the NEO instrument. It will be using licensed antisera for the 11 common antigens.

The use of different technologists and reagents: For manual testing on the first donation for negative antigens, such as if you find somebody to be Duffy a-negative, we are repeating these with another reagent and, if possible, another technologist. This is not done for automated testing. It's just done once on the donation for automated testing.

How often should typing be performed? This is

covered by two standards in the Canadian standards for blood and blood components. Standard 8.2.4 says that donor blood type for blood group antigens other than A, B, O, and D shall have two antigen typings from separate donations performed before the antigen typing is considered confirmed.

So that’s pretty clear. That’s a fairly recent standard.

Then standard 10.7.4 says that when clinically significant red cell antibodies are found or the recipient’s history contains a record of such antibodies, whole blood or red cells lacking the corresponding antigen should be selected for transfusion and shall be demonstrated to be compatible by a cross-match method to detect the antibodies, except where clinical situation justifies an exception.

How often should typing be performed before labeling, another specific question? In CBS, typing has to be performed on two separate donations, since the introduction of the PROGESA computer system, before it will be printed on the end label. If the typing was performed on one or more previous donations and on the current donation, the phenotype will be underlined on the label.

The majority of hospitals do to retype units when the phenotype is printed on the label, but they are doing a

cross-match for patients where there is an antibody that has been identified, as per the Canadian standard.

Here’s a sample label. You can see here we are both blood operators and -- I, myself, as you can see if you scan my shirt -- ISBT 128 label. Here is the ISBT label, and here you see a bunch of antigen-negative antigens. They have been done on two separate donations, because they are on the label, but they have not been done on this donation, because they are not underlined.

Here’s what it looks like on an actual unit. It’s a little bit harder to see. There’s a list of antigen-negatives over here, and there’s the barcode-readable part of it.

Tie tags: I used to think these were terrible. It turns out that even they can be not so bad. We will use tie tags. We use them if the phenotype was performed only once. Basically that’s the story. There can be several permutations of that. It can be performed only once on one previous donation and not on the current donation. That’s one possibility. It can be performed only once on the current donation. That’s once even though, as I mentioned, we would be doing it with two different reagents and two technologists, if possible. But, still, it was just done on one donation, so it’s not printing. It’s on the tie tag.

If the phenotype was performed on one previous donation and it was also done on the current donation after the end label has already been printed, you can also find yourself with a tie tag. In theory, you have done it twice, on two separate donations, and it could be printing on the label. But if you have already printed the label and put the unit in inventory, when you then get a request for something, obviously you're stuck having to put it with a tie tag or over-label, and we don't over-label.

We also do use the tie tag when the phenotype has been performed two or more times in the past. But at a customer request, they also want it done on the current donation. We have one province where hospitals have been requesting this, but they have reevaluated and this practice, not well loved by the donor testing laboratory, will be stopping in the next few months. In those types of cases, the phenotype is both printed on the unit and written on a tie tag.

This is an example of a tie tag when only the current donation was tested. There would be the donation number there. It would say that this donation has been tested. Then you would have the "negative for encircled antigens" on there. There would be a little exhortation on the bottom there to please cross-match with a fresh specimen.

This is an example of a tie tag where only a previous donation was tested. Here it says that donor records show that the donor is antigen-negative for -- and you would circle the antigens. At the moment there is an exhortation that the phenotype must be confirmed, although we're going to be revising the tags to remove that, because it's not really our place to say that. So we're going to clean that up.

You can have a mix, of course, of a printed label and a tie tag. This is an actual unit in inventory at one of our hospitals. You can see that it has a bit of everything. This one would be good on a pop quiz of every possible situation, permutation, and combination. On the label, you have an E-negative, c-negative, and Kell-negative. Those have been done more than once. The c is underlined, so one of the times it was done was on this donation. The other two antigens were more than once, but not on this donation.

There's also a pheno-tag, with a whole bunch of other antigens. It's the tag that says that our donor records show that the unit is negative for a bunch of those antigens.

What might have happened here was that the unit was put in inventory, it had its Rh c, E, and Kell done -- a lot of our units have that now, because that's coming off

our Galileo machine -- and then there probably was a hospital request for a more extensive phenotype, which is -- I haven’t added up the probabilities here. Connie would probably do it in her head, like that. But it’s a pretty rare unit, plus we don't do that much M phenotyping, because it’s usually not that clinically significant.

But anyway, this was probably a request, so we looked in our computer system and we found it, but this part had only been done in the past and it was shipped out. Maybe it was an emergency or maybe they were going to check it themselves. So you see that you can get into a pretty complicated label.

Donor identification: This is another question I was asked about. The donor is assigned a unique PROGESA donor ID during registration. That’s linked to each donation. The PROGESA system performs a check of the phenotype test results on the current donation with historical results. It will flag a discrepant result in an anomaly report, and the discrepancy has to be resolved before the components from the donation can have the label print out and be stuck on them.

Unlicensed reagents: For rare antigens, there are no licensed reagents, as we have already heard. Although we wish all patients would just hold their antibody production to antigens against which there is a

licensed reagent, some of them are not so consideration. So to meet patient, testing has to be done and the results have to go into the computer system so that we can run a report to see if we have units or if we have donors that are negative for that particular antigen.

The results are entered once into the results/test area of PROGESA. We also enter into the medical comments section a note that this was performed using unlicensed reagent. We may also put a rare donor code in that donor's file, because this might be somebody that we may want to flag the next time they come and maybe freeze their unit. On the next donation, we would find them, maybe through that rare donor code, and we would repeat the testing, but we would not enter the actual result into the results field, so that it will not actually print on the label. We would just in the medical comments say the phenotype was repeated, but with an unlicensed reagent.

So you're not losing any information here. You could search for the donor. You could now if the typing had been done once or twice. But you will not have it automatically printing on the label.

These components are issued with an accompanying letter. The letter states what reagents and methods were used. If part of the phenotype was performed with licensed

reagents at these two donations, that part could print on the label, and then the unlicensed part would be in the letter. A working group is looking at this to see if it can be a little bit better than it currently is.

This is an example of a sample letter. We had a request for Diego A-minus units. They're not rare, but there is no commercial antiserum. We state that there's no commercial antiserum. We used a human serum. It's not a licensed test. It's not going to appear on the unit label. It's not a test of record. Use your clinical judgment. All that's missing is a skull-and-crossbones thing here, as we absolve ourselves of any responsibility, to the satisfaction of our quality and regulatory affairs group. We also tell them how we did the testing. It was tested in gel-IgG, with reagent-grade Diego-positive and negative red cells, and the controls reacted appropriately.

Genotyping: When Dr. Denomme still worked for CBS, before he hightailed it for greener pastures, CBS performed a large genotyping project of about 8,000 donors. Now we do, really, a small number of genotyping tests on units where we're looking for something very specific. The genotyping tests are entered into a separate database. Some of the results eventually find their way into PROGESA, usually after serologic testing was performed. As with tests using unlicensed antisera, the results from

genotyping would not print on the label, but would be included in the kind of letter that you saw before. It would say what methods were used there in the same way.

Hema-Quebec has a very similar practice, also on ISBT 128. It’s a little bit different in that even phenotypes that have only been done on one donation are printing on the label. This is the little ISBT scheme. There will not be a quiz at the end on this, because it is a bit complicated, too. The label tells you if the phenotype has been done only once, in which case it’s the spindly print here. If it has been done two or more times, then it becomes bold. If it has been done on this donation, it's underlined, and if done only on previous donations, it’s not underlined.

Here in each of these cells you have the various permutations and combinations. I tried to write it out and found I was getting myself mixed up, and then figured a two-by-two table would be a little better way to show it.

Here is a Hema-Quebec unit out of the blood bag. Again this is a nice complicated one that is an actual unit in inventory. Here you see a mix of everything. It’s quite an extensive phenotype there. There are a couple of antigens, Kpa and Wright A, that have been performed only once on a previous donation. So they are spindly and they are not underlined. There’s one, the Colton B-negative,

that has been performed more than once, including this donation, because it’s in bold and underlined. The other things have been done more than once, but not on this donation. They are in bold, but they are not underlined.

Hema-Quebec has not done mass phenotyping with automated instrumentation, but has done more extensive genotyping than CBS, with 28,000 donors in their database. The genotype results are shown on an attached tag. They are in a separate database. The donors have the information in the comments section in the PROGESA system rather than in the results section, so it’s not printing. It’s not completely satisfactory. We recognize this. Hema-Quebec, CBS, and Health Canada, our regulator, are working together to try to find a better solution.

This is an example of the genotype tag that they are using. There would be the donor number here. If your French is a little weak, and if your eyesight is even a little weaker, what it says there is that the phenotype could not be determined because there’s no commercial antisera. The genotype of the donor is negative for the following antigens. What you have there that are kickoffs are the usual suspects for which there are no licensed antisera and where a fair number of units are being issued using genotyping results. On the top line it's the Dombrock system, and then there are a couple of the rarer

antigens in the Rh system and in the Kell system. There could be others. Then there's this little line here -- again, the sort of skull-and-crossbones thing -- that the genotype can occasionally differ from the phenotype.

In summary, the majority of red cell antigen testing is being done using licensed methods and reagents in centralized laboratories. Once units have been phenotyped on two donations at Canadian Blood Services, the phenotype will print on the label. We feel that this improves efficiency for the blood system overall, because phenotyping being performed at the hospital does not carry over, obviously, to information for the blood system when that donor next returns, while with this, we're not losing the information about that donor, and if somebody rare is identified, we then know that that's a rare donor that we want to keep in our system.

Also we know that our hospitals are sort of raising the bar on using phenotyped units for women under age 50. As I-forget-who pointed out, the standards are stricter in Europe. When you have a lot of O-negative units that also have the Kell and the RHCE on them, it's very easy to just take one that is Kell-negative and C- and E-negative to transfuse a female child or a young woman.

Tie tags and letters are being used for unlicensed reagents and unlicensed methods, mainly

genotyping. These are not entirely satisfactory, and a method to include this information on the label would be actually preferable.

I just would like to acknowledge that a lot people from CBS and from Hema-Quebec helped me in answering the rather specific questions that I was asked.

Thank you for your attention.

DR. JACKSON: Thank you very much, Dr. Goldman.

Are there questions for Dr. Goldman?

DR. SCHEXNEIDER: I find the underlining, boldface, non-boldface a little bit confusing. I think if I was, say, a bench technician that was not using phenotyped units very often, I would get mixed up. As a medical director, which is what I am, I might feel like, if I need a unit, it doesn’t matter whether it has been done once or twice or on this unit or just historically. I don't care about that. Do you get feedback from your customers on what they think about this scheme?

DR. GOLDMAN: That’s a very good point. I agree, it is complicated. It's the way the ISBT labeling is. We do not emphasize with our customers the underlined and not underlined. We communicate to them through a customer letter which we send to all of them. That’s available on our website. It explains all of this. But what we emphasize is -- and “we” is Canadian Blood Services -- if

it is printed on the label, it has been done twice. The big distinction is whether it is printed on the bag. “Label” is not a precise enough word. If it’s printed on the bag, on the container itself, it has been done twice. They don't really worry very much whether it has been done twice including that donation or not, other than one province, which has now changed its mind.

If it’s not printed on the label and it’s on a tag, then the tag explains what -- or a letter -- that is explained on that tag. The tag says it has just been done once in the past or it has just been done once on this donation, or the letter says exactly what has been done.

So I think when you think about it that way, it’s much simpler. I agree, trying to think about this donation, previous, done twice, not twice, all by the printed label is pretty complicated. That’s why we’re not having it print at all if it has just been done once, and we have gotten away from emphasis on the underlined or not. It is complicated.

DR. DIMICHELE: Based on what you have said, do you have a province-wide experiment in terms of end users that have demonstrated that -- well, I guess they haven’t, because they have been asking for it on the donation itself. Do you have any information in terms of your end users and end recipients over the time period that you have

actually been using historically labeled blood? In other words, do you know if your hospitals are largely retesting units or not retesting units prior to transfusion? If they are not retesting units, have there been any issues, any adverse events, any hemolytic transfusion reactions? Do you have any of that data?

DR. GOLDMAN: The story has been evolving, obviously. Before we centralized to the two laboratories, we did have occasional discrepancies reported to us from our hospitals -- small in number, from maybe five to ten a year. Those could have been for a variety of reasons. Part of it was that when we transferred over from our previous computer system to MAK PROGESA, the information may not always have transferred so perfectly.

Another is that antisera evolve over time. When you're using historic typing, it could be that the antisera that you used 15 years ago wasn't quite as good as it is now. Certainly for RhD, for example, it has evolved over time. So there could be that.

There could have transcription errors in the past, because we were not necessarily repeating on two separate donations in the past. That was not a requirement. It could have been just done twice on one donation.

Since we have decided that if it wasn't done

before PROGESA it does not count, then we have really not had errors reported to us. I think we have had zero discordance reported in the last year.

DR. DIMICHELE: That means they are testing, then, at the hospitals.

DR. GOLDMAN: I think approximately 60 percent of them are not testing anymore. Again, that’s an evolving story. As they have gained more confidence and they have seen there are no discordances or their budget has been tanking or a combo of both, they are just going by what’s on the label.

DR. JACKSON: In the interest of simplicity, have you considered labeling if just on the current donation or if there are two historical typing, whether serologically phenotyped or genotyped -- to just do it that way? From the end user’s point of view, I think you are really not as concerned with whether it has been done twice or once. Why not allow you to put it on the label if it’s on the current donation or has been done historically twice, as long as it has been done with a licensed or validated test?

DR. GOLDMAN: That’s what Hema-Quebec is doing. That’s where you get into the underlined and not, and it’s spindly or in bold --

DR. JACKSON: No, no, no, I’m not talking about that. You don't put any of that on there. You just say

that it’s negative for these antigens, that’s it, whether it’s done just on the current donation or it's done twice historically, whether it’s a genotyping method or a phenotyping method, as long as they were licensed assays or validated assays.

DR. GOLDMAN: There are two problems. The first is that Canadian standard which requires that the typing has to have been done on two separate donations prior to labeling. So that’s one thing. We would not be meeting that standard. That’s why it has to be done on two separate donations.

In terms of licensed reagents and methods versus non-licensed, although from a medical perspective I would love to be able to send out a customer letter -- and, by the way, the customers know that there is no licensed reagent for these rare-bird things -- they cannot repeat those rare-bird things, because they for sure don't have an antiserum that we got out of the SCARF (phonetic) program or -- I would like to do that, but I think our quality and regulatory affairs group are not comfortable with that.

But we are internally trying to find a better way. I don't think the tags are that great a way, and it’s complicated.

DR. JACKSON: I agree.

DR. GOLDMAN: And the letter is really not that

good. As others have mentioned, to have some letter floating out there that isn’t part of the bag is not really all that good. As we do more genotyping and there’s going to be more of that, it becomes more problematic. We have to think about how to do that better, I think.

DR. KUEHNERT: Has anyone looked at the error rate for a transfusion service of this sort of tie tag or sheet business, needing to tie it onto the unit or matching to the unit and just screwing it up and having it go onto another unit, resulting in a patient reaction? Are you aware of any cases like that?

DR. GOLDMAN: No, but you could easily see that it can happen. That’s why I think ultimately we would like almost everything to be printed on the unit in terms of losing the tag or the letter. Ideally, when it's printed on the unit, you can’t lose it. That’s a huge advantage of having it on the unit.

DR. KUEHNERT: I just think that’s a risk that needs to be taken into consideration. You probably wouldn’t notice. If it results in a minor hemolytic reaction or a delayed reaction, you probably wouldn’t notice it anyway, so it would be hard to measure clinically.

DR. GOLDMAN: It’s kind of a nightmare for our staff, too, when you get into the different kinds of tags

on the different kinds of bags.

DR. JACKSON: We're going to have to conclude this for our next speaker. I know some people who are speaking have to catch planes. We'll move on to Rebecca See for our next talk.

Thank you, Dr. Goldman, that was very informative.

Dr. See will be speaking on labeling with historical antigens.

Agenda Item: AABB Workgroup: Labeling with Historical Red Blood Cell Type Results

MS. SEE: First I would like to thank the FDA and the BPAC meeting organizers for inviting me to present the progress of this AABB workgroup.

As Ms. Jones said earlier, the workgroup origin did come from a previous meeting in the spring of 2012 of the AABB-FDA Liaison Committee. At that time the workgroup was given the charge to review the historical antigen labeling processes currently in use and present a protocol that would provide an acceptable mechanism for multiple establishments to use. During our first call, the workgroup decided to do the following advance work.

The workgroup decided that they were going to review the current processes in use by the workgroup members. In this case there were four blood centers

represented on the workgroup. As you might believe, they did not all agree on what a historical negative antigen was, and labeling was not managed in the same way with the four workgroups.

So they decided to get a wider sampling of how the processes performed. This is when we decided to do surveys. On the next slide I'll show you the very small, unofficial surveys that were performed.

As you can see, the information was gathered from an initial survey by ABC members that were on the workgroup. Some of this information may have been contained in what was presented by Dr. Katz, but we don't know for sure.

The survey gathered from 38 ABC blood centers. The results were that 25 use a tie tag -- again, this survey was performed very quickly -- 7 label by using packing slips, 5 only label units if the antigen had been tested on the current donation, and 1 said they put historical confirmed antigen on the label.

Then our transfusion service members on the committee surveyed 17 pediatric and adult facilities. They asked them two questions. They asked if they will accept historical testing, and if historical testing are received, do they confirm the types. As you can see, the results were: Twelve allowed units with historical testing and

only six of those reconfirmed. The reason they gave for why they reconfirmed was that the blood supplier charged extra for confirmations or the blood supplier would not confirm the results -- again, a very small group, with just a couple of our members.

The workgroup agreed that their next step was to break into subgroups. They saw little nuances and wanted to work on the issues of ensuring donor identity, labeling, defining that historical negative, what it is, and customer expectations.

So the first workgroup. Here are the workgroup projects. On the next few slides I'll detail the workgroup and what they have done to date.

The first was the one that a lot of people couldn't agree on. This is a draft definition. We have not finalized it. The bullets listed here represent the key points the workgroup is considering for the definition. Those of you who are majors in English know that if we put all this together, the sentence is way too long. We are working to finalize the definition. We were talking as of even last week about the definition.

Ensuring donor identity: We have heard a lot about ensuring donor identity. As many of you know, blood centers currently ensure donor identity throughout the donation, from the time they walk in the door, through the

manufacturing practices of the product, and that even includes the testing. The establishments are inspected and accredited by the FDA and AABB under requirements under requirements sufficient to assure the identity of the donor and donation.

This project is pretty near completion. The workgroup feels that no additional requirements are necessary to assure donor identity when labeling with historical antigen typing results. There may need to be some tightening up, but no new requirements.

The next is our labeling options. There are a lot of options that we talked about. Currently what we are considering is that when a donor unit is tested using licensed methods on the first and second or subsequent donation, this information can be used to label the units of future donations without testing of these donations. In cases where there are no licensed reagents for a particular blood group antigen, two unlicensed tests performed on separate donations may be the basis of labeling future donations. Again this is still up for discussion within the workgroup.

Potential recommendations when unlicensed reagents have been used -- this is just a reiteration of what we have heard today. Laboratories that use unlicensed reagents -- as we know, ones that use licensed reagents are

being inspected and are already doing this -- should qualify and validate their processes, include positive and negative controls with every test, and participate in proficiency testing.

What about our customer expectations? We have two members who worked very hard and surveyed some customers. These are the responses that we got. The customer expectations listed here, as I said, are more transfusion services than what was in the previous survey. A lot of them were workgroup members that have relationships with different customers.

Testing should be the responsibility of the blood supplier. Transfusion services want to receive the antigen typing results and they want to be informed when unlicensed reagents are used.

Results should be attached to the unit. Communicating the results of antigen typing on a packing slip should be discouraged in favor of using a tie tag. The packing slip introduces a greatly likelihood of error and risk to the recipient than attaching the results to the unit.

Repeat testing by the transfusion service, if done in duplicate on two donations, would be duplicative. Antigen typing is a huge expense to the transfusion service, whether they are small ones or large ones. Having

to maintain inventories of all the typing sera is the biggest expense. Some of the antisera are not available, very limited, and very expensive. Of course, as was also said in the group, in the case of an emergency, when someone walks in the door, they don't have that typing serum. This is the reason that through the years the testing has moved to the community blood center.

So what are our next steps? The subgroup projects discussed previously will be finalized. When preparing the recommendations for the agency, the workgroup will work with the FDA liaisons which are on our workgroup to present information that would assist the agency in coming up with something to help this issue.

The workgroup’s final thoughts: The practice of labeling with historical antigens has worked for decades. Bringing these practices into full GMP compliance is the goal of the workgroup. Improving patient safety is also the ultimate goal of this workgroup.

Here are the workgroup members that I would like to personally thank. The group has given many hours working on this project. In many cases we have had two, three calls a month, emails going back and forth, even on Thanksgiving. This group is very passionate and dedicated to ensuring patient safety.

Thank you again for allowing me to speak and

present. Any questions?

DR. JACKSON: Any questions for Ms. See?

(No response)

Thank you very much.

MR. DUBIN: Dr. Jackson, before you go to the public hearing, can I make a short comment?

DR. JACKSON: Go ahead.

MR. DUBIN: Most of this discussion has been about the mechanics of blood collectors and their end users or customers, the hospitals. I know when I'm talking with blood bankers, I have to change my language a little and change what we call end users -- us -- to "recipients." But the point I want to make is that I saw a feedback loop. For those of you that don't know me, I'm in radio. That feedback loop shouldn't just include the collector, the end user, without the recipient.

There's a whole question on the table that has not been talked about. I wanted to wait until the mechanics got worked through, because this is such an important discussion for everybody to have. Yet there's this question of informed consent that's lurking on the table. This morning the Committee of Ten Thousand gathered its sickle cell working group. We have sickle cell people on our board, as some of you know. They raised a number of questions. They looked at some of the public materials and

asked me to say a couple of things that I feel I need to just add.

DR. JACKSON: Corey, if you wouldn't mind, could we do the open public hearing first? I think these are important issues that we'll all bring out in the discussion.

MR. DUBIN: I'm glad to wait. I wasn't sure when to bring it up, Dr. Jackson, that's all.

DR. JACKSON: Just because we have some people who have to leave, and so I would just like to get through the formal presentations.

Next we have several speakers from the public who want to speak. I need to read this announcement.

Agenda Item: Open Public Hearing

DR. JACKSON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with a sponsor, its product, and, if known, its direct competitors. For

example, this financial information may include the sponsor’s payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of a financial relationship at the beginning of your statement, it will not preclude you from speaking.

Having said that, I think we can proceed with our first open hearing public speaker, who is Allene Carr-Greer, director of regulatory affairs of AABB.

MS. CARR-GREER: Thank you. I appreciate the opportunity to make these comments, and especially whoever thought to provide the stand here for the papers.

I don't have any conflicts to disclose.

I’m presenting the statement today on behalf of AABB, America’s Blood Centers, and the American Red Cross.

Today we have heard presentations related to many aspects involved in the practice of testing donors for minor RBC antigens, and various ways in which these results are provided along with the unit of blood to transfusion services. While there are many transfusion services that perform minor RBC antigen testing, many blood centers have assumed this responsibility. The movement toward having the testing performed by reference labs at blood centers

has occurred for a variety of reasons that we have talked about today -- rarity of test materials, cost of test materials, and availability of experienced and trained staff to perform the testing. Because of the current discussions we have been having, we also have become aware of the variability in practices and join the FDA in seeking a rational approach for the distribution of current donations with historical RBC antigen screening results.

The use of historically screened RBCs represents a long-established practice that should not be curtailed without compelling reasons. The prohibition of integral labeling of units with historical antigen screening results is contrary to current good manufacturing practices and should be remedied without undue delay. FDA recognizes that integral labeling provides the best level of safety for recipients. For example, in 21 CFR 606.121(e)(2)(ii), there’s a requirement that the name of an antibody that has been identified during donor testing be included on the label. According to another CFR section, the name of the antibody can be provided on an attached tie tag. That’s found in 21 CFR 606.121(j). Requiring that the historical antigen test results be provided on a detached report -- and, of course, Dr. Epstein has explained that there may be some issues with that as well -- requires multiple steps to ensure the same level of safety that integral labeling

would provide.

FDA inspections and AABB assessments of licensed and accredited blood establishments have shown that current manufacturing processes include the appropriate steps for ensuring that test samples and donated products are accurately linked to the donor and that this linkage carries throughout the manufacturing process.

Earlier this afternoon, there were a couple of observations. When donors present to donate, donate numbers are assigned specific to the donor after the donor presents identification. There are not specific requirements for how donor identification is assessed.

That’s true. There is not a requirement that a donor has to present a specific type of identification. However, while there is not that requirement for a specific donor identification tool, there are requirements and recommendations that establishments must have processes to review prior records of the donor for any deferrals that are still active, deferrals related to any number of things -- medical histories, infectious disease test results, anything that would be active in a donor record that would make the donor not eligible for donations. Therefore, establishments have determined donor ID processes that work in their establishment or their community. This process is inspected as a part of FDA

inspections or AABB assessments.

There was also an observation about linkage of the donor, that this should be traceable both forwards and backwards throughout processes. Again I would note that establishments already have to have these processes to reconcile these issues, even when there is the possibility of duplicate donor records. Donors often change their names for a variety of reasons. They don't always include marriage, which would be the common thing. Again, establishments are required to have processes to reconcile these issues, and these are looked at in inspections and assessments of blood center establishments.

Furthermore, FDA has acknowledged the robustness of this process to encompass labeling with historical test results by accepting the following language developed for the circular of information: All blood has been collected from donors who have tested negative by a licensed test for antibodies to *T. cruzi* either on the current donation or at least one previous donation.

We believe all of this supports the fact that there is no need for further validation of processes currently in use for linkage of donor ID and test results, current or historical.

We encourage the FDA to allow and assist the AABB workgroup in completion of their work –- that is, currently

focus on assuring the quality of the antigen typing results -– and to carefully consider the draft protocol that is developed. We also request that the agency provide a route for all blood establishments to use whereby historical results can be properly attached to the current donation.

The remainder of the statement describes the organizations who have developed and support the statement.

Thank you.

DR. JACKSON: Thank you very much.

Dr. Richard Benjamin, chief medical officer of the American Red Cross Holland Laboratory, will be our next speaker.

DR. BENJAMIN: Thank you, Dr. Jackson. Kathy Kaherl will be giving the Red Cross presentation.

MS. KAHERL: I have no disclosures or conflicts.

Good afternoon. I want to thank the committee for the opportunity to share the American Red Cross perspective regarding the labeling of red blood cells with historical antigen typing results.

The American Red Cross biomedical services mission is to fulfill the needs of the American people for the safest, most reliable, and most cost-effective blood services through voluntary donations. We distribute approximately 6 million red blood cells and 850,000

platelet products every year. We perform ABO and RhD typing by automated methods in five national testing laboratories.

To fulfill hospital requests, we perform greater than 600,000 antigen types each year in 40 IRL locations, using mostly manual methods. In the last year, we genotyped greater than 25,000 donors at one laboratory.

In calendar year 2000, the American Red Cross instituted a review of all antigen typing mislabeling errors. After the review, a standardized corrective action was implemented that required two antigen typing results for labeling. The two results could be two types on the current unit using different segments or it could be one antigen type on the current donation and one result from a previous donation. A labeling review step by a second staff member was added.

A national procedure was instituted in 2002 in all IRL locations, and revisions for continuous improvement followed.

Our testing process for labeling is shown here. The first time a donor is antigen-typed, there are two paths that can be followed, shown here on the left-hand part of the slide. The first path could be two serologic types performed on different segments. The first test within these two types is considered our preliminary test

and is performed by tube method, using licensed or unlicensed antiserum. The second test is indicated as the test of record and is tested using licensed antiserum, if available, and is indicated on the tie tag. An example of the tag will be shown on the next slide.

If licensed antiserum for a particular antigen is not commercially available, then unlicensed antiserum trying to use a second source may be used. This information is again conveyed on the tie tag.

The second path that a donor can follow the first time they are antigen-typed allows for one molecular test and one test of record, which is the serologic confirmation as described in that first column. A subsequent donation for a tested donor is shown in the column to the right. The donor will be tested with one test of record type and a verification of the historic type that occurs during second-person review of testing.

This is our current antigen typing tie tag. As you can see, there is an area to communicate the antigens that were tested using licensed antisera, as well as an area that indicates testing performed using unlicensed antisera.

After testing is complete, our process continues with a review of testing by a second person. The unit is tagged with the pertinent information after testing review

has been completed, and then the tagged unit is reviewed, utilizing a verbal confirmation of the unit, the tie tag, and the testing paperwork concurrently with two staff. If serologic testing is not performed on the current unit, the molecular or historical serologic information is provided to the customer in writing by way of a report that accompanies the product, but is not affixed to the unit. Also this is reviewed by a second person.

Historical types are established in the computer with two types, one of which must be a serologic test of record result or one molecular test. The computer entry is reviewed by a second person. Our current practice for product labeling requires a test of record on the current donation, in addition to the historical type.

This slide shows the rate of events involving mislabeled antigens. In fiscal year 2012, which was 12 months, eight events were noted out of 601,926 antigens tested. This represents 0.13 events for every 10,000 antigens tested. In calendar year 2000, prior to our standardized approach -- and that represented eight months of data -- there were 17 events noted out of 238,127 antigens tested. This represents 0.71 events for every 10,000 antigens tested. The difference in the two reporting periods after the standardized process was initiated is shown as a reduction of 0.58 events for every

10,000 antigens tested and is highly significant using a normal approximation to the chi-squared test and Yates' correction. Stated differently, there is a 99.9987 percent accuracy for our current process during the last reporting period.

The American Red Cross would like to make the following recommendations. The FDA should allow the use of direct labeling using historical types, with the following criteria -- first, regarding the establishment of the historical type:

• Each donation tested at least twice. Two separate donations would not be required.

• Different segments or samples must be used when testing the same donation.

• A licensed method following manufacturer's directions is required, using in-date reagents without dilution.

• Licensed reagents must be used when commercially available.

Continuing on with the establishment of the historical type, in addition to the criteria on the previous slide, unlicensed molecular testing can be one test method. For those antigens for which only molecular methods are available -- for example, Dombrock and Halley (phonetic), and you have seen other examples earlier

today -- label the red cells with a tie tag indicating testing performed by laboratory-developed molecular method only. Finally, the molecular result can be from a current or historical donation.

In addition to the establishment of the historical type, labeling must be performed by a GMP-compliant process with positive identification of the donor and the use of a quality system to establish historical types, eliminating the need for repeat typing of the current or future donations.

Thank you for your time.

DR. JACKSON: Thank you very much.

Our last speaker, Dr. Connie Westhoff, director of immunohematology and genomics, New York Blood Center.

DR. WESTHOFF: Thank you for the opportunity. I also have some slides.

I would like to briefly detail the New York experience using historical antigen types. I'll remind you that New York Blood Center is one of the largest community-based nonprofit blood group collection agencies in the US. We annually provide about 1 million components, including 400,000 red cells, to about 200 hospitals throughout New York and the underlying areas. The population served by New York Blood Center exceeds about 22 million people, and we are actually home to the largest single institutional

frozen red cell inventory, over 7,000 rare, which means that it occurs in fewer than 1 in 1,000 antigen-negative units, or uncommon, meaning they are multiple negatives for multiple antigens, in our frozen inventory. This has been amassed through a very active program of more than 15 years of typing donors for minor and rare red cell antigens.

Part of the issue for the New York Blood Center is actually the testing and labeling over these 15 years and devising a process by which this is done electronically. We type about 700 donors a week. This is serologic typing. We type over 200 donors a week by molecular. I'm not going to talk too much about molecular, because we keep that in information in a separate space as an unlicensed test, and we purely use that for screening and confirmation. I'll show you in a few minutes what else we use it for. But it's kept in a separate database as an unlicensed test at the current time.

Historically, in 2011, 82,000 of our 396,000 donations had actually extended typings on them. Greater than 20 percent of our inventory is completely typed out at any time for these 11 common antigens. In 2011, 18,200 antigen-negative products -- that's units, not antigens -- were provided to our customers. This graph shows you how this need is growing. In 2000 we distributed 10,000 units, and in 2012, we will have distributed over 20,000 antigen-

negative products -- a 100 percent increase since 2000.

This increasing need for antigen-negative units, we predict, will continue to grow. You have heard from Lynne and others about the prophylactic use to prevent alloimmunization, to prevent delayed transfusion reactions. Production of an antibody increases the cost of treating the patient, the workups, et cetera, and increases patient morbidity. Especially with the growing focus on an outcome-based compensation model at the hospital level, we feel this need will only grow.

We also feel strongly that antigen testing is much better done at the donor service rather than in the hospital transfusion service. Why is this? Because we have automated high-throughput instruments we can use that directly download the results to the computer system. We can actually label these units electronically and not by hand. We can associate the results with the donor. That's very important. Typing done at the hospital level is lost information. It's not linked to the donor. It has to be done over and over and over again, which is a very repetitive, expensive cycle.

We contend that it's much less expensive to do at the donor center. Most of our requests are for three antigens, C, E, and Kell, or more. We estimate the hospital cost at at least $25.50 for just reagents without

labor to find one of those units that are negative for C, E, and Kell. The cost is actually often more. It depends upon what is present in the hospital's inventory to find those units.

How do we do it? I'm sorry this is such a poor picture from my cell phone. We use the PROGESA computer system. We have gone to ePROGESA now, since January of last year. We generate electronic barcode labels. The tie tag that is attached to the donor unit actually bears the barcode of the donor unit. Labeling, then, is a manufacturing process. We label either results from the current donation or two concordant results from two separate previous donations. The computer actually detects and flags any discordance between those two tests. The labeler is the one indicated by the "Reviewed by" there. This is a computer-generated label that is checked, barcoded to scan the label and the unit and the actual results -- comparison between the tag and the computer.

The other thing we do is we only carry negative results forward to cut down on the data we have on a donor. Positive results aren't what you are looking for anyway. We don't want a positive. So we only carry the negatives forward. You see a positive on this label here. That means it was done on this current donation. When there is a second hit on that full phenotype, only the negatives

will carry forward. We feel that this is going to help us when we go to the barcode label in the small area that's available on the ISBT tag.

For rare and uncommon units with no licensed reagent, that actually represents 2 percent of the units we provide. We also provide HPA-1-negative products. That's a labeling issue -- also platelets. Our policy is that the test, if it's unlicensed, is put on the label. If it's done by DNA or serology, it's considered -- either DNA or serology, as long as it's unlicensed, it's unlicensed. It's actually just stamped on the tag.

DNA testing now is done for most of these rares because we have very few in-house antibodies left for doing these typings.

Again, it's the same rule: two types, concordant, and it carries forward historically. Testing is not repeated after two donations are concordant.

We also think HLA labeling of platelets is a topic maybe that should be discussed here also. HLA typing of platelets is just done one time and results are communicated on the paperwork for most institutions.

Just a couple of points I think the committee has run into. The first one is that all results that the industry is calling historic are not equal. It's a terminology issue. Having worked in three or four

different regions of the country, “historic” in the Midwest means something very different than “historic” in the East or West. In other words, some historical results were never intended for clinical use without confirmation. They were intended to help the hospital find what units to start typing. These were provided for a nominal fee or at no cost on a packing slip. Those industry folks didn’t intend it to be used for clinical. They intended it to be confirmed.

This is in contrast to high-confidence historical results talked about here, which are confirmed and found concordant on two donations.

So one of the tests of the committee is to clearly define what “historic” is meant.

We are encouraged because the ISBT now allows labeling with historical information, although the process is somewhat cumbersome, as you have seen from the Canadian experience. The new September guidelines actually suggest a 2-D barcode and that those bolds and underlines are replaced with comments in 2-D barcode that are seen on the screen or on accompanying material. But the label actually looks all the same.

As far as the CFR 40.4 and 40.5 that says all laboratory tests should be made on a specimen of blood taken from the donor at the time of collection, we

certainly do all our minor antigen testing on blood taken at the time of collection. We don't call a donor in and especially type him. Everything we do is linked to the donor and linked to the donor record electronically at that time.

The last thing I would like to point out is that the perception that testing done for minor antigens that aren’t done on that donation may be inferior I caution against. It may be a misconception. It depends upon the system and the process used.

Looking at our experience suggests otherwise. In fact, we looked at a three-year period, 2009 to 2011, 125,000 antigens retyped by hospitals. We surveyed our hospitals and said, who is retyping? Eighty-five percent of our hospitals were retyping. We said, why are you retyping? Do you not trust our results? Have you found errors? Don't you report the errors back to us? They said, yes, we report them back to you, but we thought the New York state reg required that we do this. Well, it doesn’t.

So sitting down with our customers, we have shown them what our discrepancies are. For 125 antigens, we had seven discrepancies. Five of them were weak variant antigens that weren’t detected by one manufacturer’s licensed reagent. That’s an issue that we all know exists.

One C typing was a false positive. The actual reagent was detecting a false positive. There was no C antigen present. Only one antigen typing left the blood center as a data entry error, and that was on a first test.

Molecular typing would detect all these weak variant antigens.

The other point is that .005 percent were discrepant, 1 in 17,994. Actually, that M antigen error was a first-time test. The first-time test in our hands, when we go back and look at the data -- when we compare first-time and second-time tests, our error rate is ten times higher. In other words, we have higher confidence, actually, in doing two tests on two different donations and having them concordant than, necessarily, the first-time test going out the door. But either is very safe.

New York Blood Center strongly supports labeling with historic types, as long as that is qualified to be a confirmed type and not something that was never intended to be used for clinical use, that was just a screening on a packing slip. In fact, we suggest it be performed on two donations found concordant for labeling, et cetera.

Thank you.

DR. JACKSON: Thank you very much, Dr. Westhoff.

Is there anyone else from the audience who would like one to two minutes to address the committee? Then we

can just open it up briefly if there are any questions for the three speakers who just presented.

(No response)

Are there any questions for any of the speakers from the public.

DR. DIMICHELE: Yes. My question is for the American Red Cross. I just would like to ask questions because obviously your recommendations are somewhat different than what we have heard from other countries and certainly what we have just heard from New York Blood Center, et cetera. What was your process before 2000? What was the major change from before 2000 to after 2000?

My second question is, why do you still think that each donation needs to be tested, if I understood what you were saying -- you did not say that?

MS. KAHERL: No.

DR. DIMICHELE: So every donation is not tested. The current donation is not tested.

MS. KAHERL: No.

DR. DIMICHELE: Okay. It’s not.

MS. KAHERL: No. Let me go back to the first question you had.

Prior to 2000, the 40 different IRL locations each had separate processes. They had local procedures, and the testing was varied. It was at that point that we

looked at it system-wide to see what we could do to shore up some of the antigen typing discrepancy issues we were having. That is when we instituted a national procedure that all IRLs followed that had robust testing reviews, labeling reviews, and requirements for two tests. That is currently what we are doing. That is not what we are advocating for the future.

DR. DIMICHELE: But you are saying that you can do those two tests just from two different samples on the same unit.

MS. KAHERL: Yes, we are. That is our current process.

DR. DIMICHELE: Then I misunderstood something. Thank you.

DR. PIPE: I also misunderstood the one point. If a historically verified testing -- you feel that it’s confirmed. You are proposing that it be carried forward to all subsequent donations. What does a test of record then mean? You still included that a test of record must occur on the current donation. What does a test of record mean?

MS. KAHERL: What I’m showing you right now is our current process, in 2012. A test of record is tested for each donation for the antigens, if it’s to be labeled. That is just our current process. We have not changed our process to include historic labeling, because that has not

changed from the FDA yet.

A test of record right now on a current donation is either two tests, if the donor has never been typed for that antigen -- it’s either two types on two different segments or it is a historical record from the computer system and a serologic two-test method for current labeling.

DR. PIPE: I think I understood that. If you have a patient that you know and have confirmed, historically and on previous donations, is Kell-negative, under your current processes, if they give another donation, you will still feel compelled to test them for Kell yet again.

MS. KAHERL: Yes.

DR. PIPE: The reason for doing that, if I understand, is purely to verify that the patient who is giving the donation that day is actually that patient. What else would be the reason for retesting them a third, fourth --

MS. KAHERL: The way we have interpreted the FDA regulations.

DR. PIPE: I just want to make sure I’m understanding. The law is purely to consistently establish the link of that day’s donation with the historical record of the patient.

MS. KAHERL: Correct.

DR. PIPE: This really has nothing to do with the mechanics of the test or the variability of the test. This is purely a linkage issue.

MS. KAHERL: Yes.

DR. PIPE: That’s not true?

DR. EPSTEIN: The regulation antedates use of historic information. The idea was simply to assure that the information is referable to the current donation. It’s sort of twofold. It’s accuracy -- because you have just done it -- as well as linkage.

DR. PIPE: I guess I understand that. But essentially everything is historical information. By the time it gets to the bedside of the patient, I, as the prescriber, am relying on historical information that that unit came from that patient, too. So I'm not sure that I understand --

DR. EPSTEIN: I guess what I’m distinguishing is the linkage issue from the belt-and-suspenders issue. In other words, it’s a dual verification. Yes, you may have historic information, and we want to verify that it’s all in alignment. Think of it as confirmation. It’s not just about linkage. It’s about confirmation.

You could say that there is only a confirmation issue when there’s a linkage issue, but that’s not true.

There can be inaccurate testing along the way, too. There could be mix-ups. There could be recordation errors. There could be failure of reagents. There are many reasons to want to confirm.

That’s the argument that you heard about ABO. It’s a belt-and-suspenders argument to really confirm it on this unit, because the risk is so high.

DR. PIPE: I would flip that around just to ask -- we don't repeat the testing on the recipient immediately before the transfusion. Is that correct? The historical record for the patient is that they are a Kell-negative patient. This is the recipient I’m talking about. You are going already by the historical record of that patient, that they are Kell-negative, who is about to get that unit.

It just seems we’re applying a separate standard for the transfusion product than for the record of the recipient.

DR. EPSTEIN: Well, that’s yet another issue. We can put that on the table if you like. I’m simply trying to explain that if there were no issues of accuracy of tests and if there were no issues of linkage of results, we wouldn’t be here having any debates. But because there have been issues of linkage and because there have been issues of accuracy, the notion has always been to confirm

the current unit, because that's your greatest level of safeguard.

That's why I'm trying to distinguish. Yes, there is an issue that additional testing confirms linkage. But it's also a belt-and-suspenders attitude toward accuracy. That's really all I'm trying to say. Let's be real sure, is the idea.

DR. JACKSON: The Red Cross position, as I understand it -- not what you are doing now, but in the future what you are recommending -- is that in order to be able to put the information on the label of what is antigen-negative, you're proposing that it be done either on a current donation that has been tested twice, if they have not been tested before, or two confirmed historical typings in the past, and you wouldn't have to do it again on the current donation. Is that correct?

MS. KAHERL: That is correct.

DR. JACKSON: And your historical donations -- the safeguard there is, if there was a discrepancy, the computer system would pick that up right away.

MS. KAHERL: Yes.

DR. JACKSON: The confidence that you have that with the current donation, the donor is linked directly to the historical types is what?

MS. KAHERL: All of our processes, from the

minute the donor walks in the door through the manufacturing processes. That linkage is there through the computer system, through a unique donor identification that links forward and backward.

DR. JACKSON: So if there were different names because of marriage or whatever, it would just tell you, at least initially, that this would be a new person, and so you would do it just on the current donation at that point.

MS. KAHERL: Yes.

DR. JACKSON: Any other questions?

(No response)

We have a break now. Come back in 15 minutes. Then we have about an hour for discussion.

(Brief recess)

Agenda Item: Open Committee Discussion

DR. JACKSON: I do want to remind everyone that the FDA is not seeking advice or recommendations from the committee on this topic -- the FDA is asking for advice or recommendations on this topic. There’s another topic right after this that they are not. It’s more of an update.

At this point it’s really open for discussion, for the committee to address the questions that have been posed. I know, Corey, you had some points you wanted to make before we get right into each question.

MR. DUBIN: Thank you, Dr. Jackson.

My goal is not to distract from the issue. As I was saying earlier, we convened our sickle cell working group at the Committee of Ten Thousand this morning, early, and had about a two-hour discussion. A lot of strong comments came back from our sickle cell members, which aren't as large as the hemophilia members in the group, but they have been with us for almost 13 years.

They asked me to remind the committee that even though we're talking about labeling and how the mechanics happen, there are serious informed-consent issues here, as they see it. They describe it as "we're 15 years behind you guys," meaning hemophilia. We understand and have watched as they are subjected to some pretty serious institutional racism as part of this equation.

I think, although we're dealing in labeling, we're still dealing in communication down a feedback loop from blood collector to hospital end user to recipient. There's a discussion of risk landscape with recipients and all kinds of things that we don't feel should be left out of this discussion.

I'll just quote one quote that came from an individual -- someone you know, Larry Allen, who sat on the Advisory Committee on Blood Safety and Availability. He said, "We are quite tired of being second-class citizens in world-class institutions. We see how the cancer patients

are treated around pain. We see how others are treated. And then there’s us.”

So I think when we talk about informed consent, even in hemophilia, I think with the younger generations we have problems, but nothing like what we see in sickle cell and we’re trying to help Equal Voices, which is a small nonprofit growing in sickle cell, to address.

Thank you, Dr. Jackson.

DR. JACKSON: Just to follow up quickly, though, the informed-consent issue is regarding consent for what, specifically?

MR. DUBIN: For instance, I don't think most recipients want to know if it’s a validated commercial assay or a commercial test, but I think they do want to know a lot about what testing has been done to ensure it’s safe and what risks exists. I think we have to continue to strengthen that part of the feedback loop. Again I go back to my radio analogy. I see you all working hard on the feedback loop, the arrows up and down between the blood collector and the hospitals and those that are transfusing the patients. But I don't see that next link in the feedback loop that is the patients in this process as part of it.

We had to fight for years to be stakeholders at this point. We’re here now. But I think the issue of

informed consent underlies more than maybe you all always see.

DR. KUEHNERT: I just want to add to that -- because it concerns what would the issue be with informed consent here -- I think one thing I haven’t seen is what the clinical implications are of having a unit that has an antigen that is not picked up and the patient has a hemolytic reaction. How bad are the hemolytic reactions compared to an ABO incompatibility? What are the implications besides the person developing an antibody?

I think that’s important in terms of thinking about some of the concerns about false negatives in the testing. What actually is the clinical implication? I think that’s missing a little bit in what was talked about here. As I said before, what I’m trying to do is compare the risks of that to the risks of errors occurring because of the typing not being on the container label, but being on the tag, being on a package sheet, and there being an error from that.

It’s hard to weigh some of these things without knowing some of the clinical implications, which the patient needs to be aware of.

MR. DUBIN: And just to add something, Matt, what about the question of delayed hemolytic reactions and the fact that we don't have a lot of good reporting, and we

don't even have a lot of good discussion with recipients about that, as far as we can see in our discussions in our area.

So that’s of concern as well.

DR. JACKSON: We didn’t talk that much about the benefits, from the transfusion service and the patient perspective, of having this information available so that these units are readily available. I can tell you, I’m a transfusion medicine attending at Johns Hopkins -- I was on last week -- in Baltimore. The majority of the population is African-American in Baltimore city, so we see many, many sickle cell patients, for example. We do red cell exchanges on at least ten a week, probably one a week as an emergency transfusion for acute chest syndrome or stroke, in which they are going to require ten units. They often are alloimmunized, and we need to provide phenotype-compatible, or at least antigen-negative, blood. If you have acute chest syndrome or you are having a stroke, trying to stop that from progressing or get a little better, getting those units to that patient quickly is very important. So the blood bank not having to retype these is a major advantage.

The other thing we have seen a lot recently, with all the same-day surgery patients being admitted the same day -- and we don't get the sample for type and screen

until that morning -- they are already going to the OR and we're trying to type and screen. If we find that they have an antibody, trying to find an antigen-negative unit quickly to get it right up to the OR is a real benefit of having this information that comes with the units that are already in the blood bank or where we could call the donor center to get those units as quickly as possible.

So there are some major, major benefits of having this information available, even if it's historical or current donation. I think there are some tremendous benefits to the patients.

MR. DUBIN: Dr. Jackson, you touched on one thing that came up this morning as well. Larry Allen talked about the stratification of care in the country. South of the Mason-Dixon Line, they found care better. He talked about the fights he had over phenotyping with certain centers where they were being treated and the pushback and how basically they are looked at, coming in the door, as drug addicts. That came up a lot. That issue relates to perception of people and a number of issues.

I don't think that's a committee decision. I'm just throwing that out there to say, if we grow informed consent there, not only is the medical and clinical benefit great, but maybe we start to fix that problem just a bit.

DR. JACKSON: I think you saw some of the data

today that there has been a tremendous amount of progress in trying to provide the most compatible blood for sickle cell patients and preventing alloimmunization -- much more than we did ten years ago. There has been tremendous progress in this arena.

I do think health-care providers are really trying to do a lot for these patients, who have very serious illnesses, obviously, and are very difficult to manage, for a number of reasons.

Why don't we get to the -- in the first topic, we’re being asked to comment on the effectiveness of the following practices to mitigate the risks related to historical antigen typing. Let’s go with A, reporting such information on the basis of historical RBC typing results from two separate donations.

Discussion or comments about this? We heard from a number of speakers and saw from a number of different countries that this is being done at a number of places, in terms of, for example, the two separate donations historically, and they are labeling the bag in some cases with that.

DR. PIPE: Related to that point, the extra verification that is always implicit in that process is the cross-match before donation. We didn’t talk about this specifically, but related to what Matt was saying. If

there was a mistake, if there was a major mismatch, it should be picked up at cross-match. If it's weak or the patient has lost antibody, yes, there's still a risk for a delayed hypersensitivity reaction, but that involves multiple errors along the way. If we're just talking about how valid this process is for establishing that that unit is as suitable as you could provide for the clinical situation, then I think it's a valid process, from what we have been shown. Then you still have the cross-match as the backup.

DR. JACKSON: I think the cross-match is extremely important. I guess the worst-case scenario is that somebody has a Jk^a antibody that's not demonstrating at the current time or we don't know about it because they come from somewhere else, and it wasn't typed correctly and they had a delayed hemolytic transfusion reaction, which could be quite serious with a kid, potentially, but it would be more likely delayed. It's unlikely that it would be more than one unit. There clearly is some risk there, but there are a lot of benefits, on the other side, as I just mentioned.

Susan.

DR. LEITMAN: There are a couple of things I want to bring up. From the discussion this afternoon, there are two things I find somewhat unacceptable, and I just want to

put them on the table.

I would like to remove the impression or feeling or risk-mitigation strategy that there needs to be reconfirmation of red cell antigen testing at the hospital or transfusion facility. Some larger university, resource-rich departments universally do this, from what we heard. Smaller hospitals without resources don't do this, giving the appearance of two levels of care. Two levels of clinical care always bothers me. What we come to today hopefully will be a recommendation so that the transfusion facility and their risk-management people feel no reason that they have to repeat antigen testing that’s provided from the blood collector, the blood center, by whatever recommendation we provide to the FDA.

The second thing -- and this is something Lou Katz discussed, but it still bothers me -- providing information that’s specific to a unit -- not educational, not general, not our policy, not definitional -- something that’s critical to patient care related to that unit should not be separate from that unit. That’s crazy. That’s high-risk. It shouldn’t be in the same plastic bag. It should be integrally connected by a rubber band restraint and should be connected to that unit. The possibility for error when you are getting shipments in a box of lots of units, lots of plastic bags being opened, things moving

around on a counter -- this has to be an unsafe practice.

I wanted to bring those two points up.

DR. STOWELL: I would like to second the second thing that Susan said in particular and go farther and say this information should be on the base label. This is critically important information, and that’s where it belongs. With ISBT 128, there’s a mechanism built in to do this. I think we would be silly not to take advantage of it.

The other comment I want to make is, we’ve been talking about risk mitigation, with the implicit gold standard being the confirmatory typing being done on that particular unit. That process is no more immune to error than having done that same process on the prior donation. That gold standard is just as susceptible to having samples mixed up, reagents not functioning, and all the rest of it.

I think comparing that to having done the typing, with whatever means, twice before is a far preferable and far higher standard, in terms of quality of the result and also addressing this linkage issue.

DR. JACKSON: So what would your opinion be about, if there’s only information on the current donation, it be tested twice on two different segments?

DR. STOWELL: I'm not sure how I feel about testing twice on two different segments as opposed to two

totally different donations.

DR. JACKSON: No, but if you only have the one donation, from the provider and the patient's perspective, that information is still very helpful as opposed to no information.

DR. STOWELL: I could see labeling that unit, but that donor, when they came back the next time, would have to be retyped. If that was a concordant result to that first donation, at that point you could label on the basis of historical type.

DR. JACKSON: Then you would have two different ones, right.

Toby.

DR. SIMON: I was impressed also that we already have a working group that's working through this. I would like to commend both the FDA and the regulated industry for establishing this group. I think they can then go through the process, hopefully based on the recommendations we come up with today, to have a system in place that will accomplish what we want -- things like Susan mentioned, that it would not be incumbent on the transfusion service to repeat.

I do think the first two bullet points go together quite well. I think we do need a basis for the historical typing. You have indicated the tremendous

urgency from the clinical point of view to have that information when we have clinical situations. At the same time, I think the second bullet speaks to the risk to the patient and that we have to make sure that the process is validated so that we can have confidence that it is accurate.

In terms of your other question, I guess I would see treating the current donation perhaps differently than the historical information, and then perhaps treating that as we ordinarily would, where we would get a type on that and then proceed to cross-match accordingly. But then we would need a second typing in order to make it historical.

DR. SCHEXNEIDER: I would like to say a couple of things. One, I strongly support the two separate donations to establish someone’s historical typing. I don't like the idea of two segs on the same unit, and then we have to -- what we do if it’s someone’s first time. We may be pressed to do that, but I would certainly prefer two separate donations.

DR. JACKSON: Let me just clarify. On the current donation, you would not want that information on the label, then, if you just had the typing on the current donation?

DR. SCHEXNEIDER: If it was a first-time donor, first time being phenotyped.

DR. JACKSON: How would you provide that information?

DR. SCHEXNEIDER: Perhaps on a tie tag. I'm thinking more about the regular donor, and if we have two historical types, then I don't see the need to keep doing it on every current donation. But maybe the tie tag would be the best option in my eyes, if it's the very first time being phenotyped.

The other thing is -- to maybe tie into what Dr. Leitman was saying -- I kind of draw a line in the sand on where we trust but verify. That's on ABO typing of red cells. That's where everybody does it the same way. At our blood bank in the military, it's probably done three or four times before it gets into the transfusion service at Walter Reed Bethesda, but we still redo that. And I support that.

But that's the line in the sand for me. If we get a unit of red cells from Susan from NIH and she's implying that it has been tested and it's HIV-negative, we believe her and we don't retest it. Nobody does that.

So I put the antigen typing in that same category. If it's not the ABO type, if it's labeled, it should be good to go. Just because we can fairly easily reconfirm that doesn't mean in any way that we need to do that.

DR. JACKSON: Let me just go back to the current donation and talking about the tie tag. I think Susan brought up the point about now we're dealing with more of a manual operation. From the transfusion service perspective, whether that says E-negative antigen on the label or on the tie tag, I think it will be treated the same. I think the advantage of making it on the label, even if it's on just the current donation and the first-time donor sort of thing, is there is less error when it goes to printing on the label -- because this is computerized -- than somebody manually trying to circle this. I still think there are some big advantages to putting this information on the label, to minimize the risk of human error.

MR. DUBIN: I couldn't agree more. Back to what Susan said about the absurdity -- that's my word, but that's what I heard -- of having a separate letter not connected, I would go even farther and agree with you, Dr. Jackson, that it should be on the label. The advantages are clear. And if this is all about building trust, which I think, in part, it is, on the label is going to build more trust certainly, from our perspective. Knowing that, communicating that to the groups within our larger group that depend on components, this is an important step of trust.

DR. KUEHNERT: I understand what people are thinking with this whole “we’re not absolutely sure, so we’re going to put it on a tie tag.” But I think you’re right, at the hospital level, all that is lost. You could say, if we’re really, really not sure, we’ll write it in crayon. But I don't think that’s going to help anybody, and in the end, they are going to try to read what it says in crayon.

I think you are trying to make this a little bit too granular for people in terms of the certainty of the result, when, really, you just have to decide, okay, what is the threshold where you can put it on the label? Otherwise, just don't put it anywhere, because it’s only going to confuse people.

The other point where I need help with clarification is these two issues, A and B. People are saying they would like to see it on two separate donations. Is that a separate issue from making sure that it’s the result of that donor? Because it sounds like that’s covered in B. If you absolutely sure that that historical result was from this donor, then would people be still very adamant about it needing two separate donations? Then, I guess, that’s an issue of how the test was done.

I would be comfortable with two separate donations, from a standpoint of validating that that’s the

donor. But if you know that that information is accurate, then I'm not even sure it needs two separate donation testing, necessarily, if those results are not likely to change, since they reflect the underlying genotype of the donor. If there's an issue about the testing and that the phenotype might not be consistent, then I would say there's a reason to test it twice. But as we start to talk about genotyping, obviously that's not going to change, and you would only need one test, from my perspective.

DR. JACKSON: But you could argue that not all phenotype results are of the same strength or positivity or whatever, and having two separate donations that are at least consistent would give some reassurance, where it might be the same, even though it's from the same donor --

DR. KUEHNERT: If there are inconsistencies in phenotypic testing, and that's the reason to do two separate donation tests, then I would be in favor of doing that. But if it's the issue of whether it's really the donor or not --

DR. JACKSON: I think that's a concern. I don't know --

DR. KUEHNERT: There are probably better ways to assure that it's the same donor. That's all I'm saying.

DR. GILCHER: I like the idea of having two separate donations to assure that we have the right donor.

But the unit can be used regardless, as long as we do the typing twice on the same unit, if there's no prior historical. That's the first point I want to make.

The second point is that I think it has to be electronically transmitted from the computer and printed. Now we have eye-readable and machine-readable. I think both of those should be present, eye- and machine-readable. That demands, then, that it be printed by the computerized system.

DR. JACKSON: Any other comments?

(No response)

It sounds like there's a fair amount of support for the two separate donations and trying to keep this, whether it's on the historical or on the current donation, on the label, if possible, and doing it electronically to minimize any human error and to give you more assurance about the donor identify as well, I think.

The third question is people's opinions about the need to confirm the relevant negative antigen results. I guess we were talking about that as part of this, about whether we need to -- would our response vary if serologic or molecular testing or both are performed. So in terms of the issue we just talked about, use of historical data, does it make much of a difference if it's serologic or molecular genotyping.

Do people have an opinion about that, and as long as we're on that, whether it's a licensed test or a non-licensed test, as I think Susan brought up, as long as it's a validated -- we do have many actual tests that we use in clinical care that are not FDA-approved, obviously, but do need to be validated, according to CLIA regs and such.

Toby.

DR. SIMON: One issue on the unlicensed test -- I know that clinical laboratories, of course, use unlicensed tests, but they usually have language that goes along with the result to indicate that that's the case, that that's a test that is not licensed -- at least the lab reports that I have seen and the labs I have been associated with. I guess that would be a question, how you integrate that in.

I do think that we should accept that molecular testing is here. I wouldn't change my opinion if molecular testing were used. It sounds like it's being confirmed. That is, you would usually have one molecular test and one serological test, presumably licensed, if available, for the two tests. But I think molecular is here and would hopefully be coming.

I don't know how we deal with the issue of including in our label that unlicensed tests were used. Maybe it's not practical in this situation.

DR. JACKSON: Other comments on this? Susan.

DR. LEITMAN: Question 2 says, “Comment on whether your responses to the first question would vary if serologic or molecular testing or both were performed.”

My answer is, no, they wouldn’t vary. But I would prefer two different types of testing in order to be maximally assured that the antigen typing that I see historically is correct. As multiple people have said, as long as it’s a validated technique, molecular testing -- I don't really care right now that it’s not a licensed technique. I would rather have a serologic and a molecular unlicensed than two serologics, because I think they are more complementary and they offer different information, and you are more likely to get a maximally accurate historical type.

DR. JACKSON: You are recommending that it be based on a serologic and a molecular.

DR. LEITMAN: I don't think I can recommend that now. I’m not sure --

DR. JACKSON: But that’s your preference.

DR. LEITMAN: That would be my preference. But it wouldn’t change my answers to 1, A, B, or C.

DR. JACKSON: So you would accept two serologic results.

DR. LEITMAN: Sure.

DR. JACKSON: But you’re saying, ideally, it

would be nice to have a molecular and a serologic.

Other opinions on this?

The data looked very good in terms of the very small discrepancy between serologic and genotyping.

Matt.

DR. KUEHNERT: I don't think I know enough about the genotypic methods to know whether you need both or one is preferable to the other. I think with time, the genotypic methods are going to be preferable, actually, but we're just not quite there yet, and they are not licensed. So I don't have an opinion on it.

The only other thing I want to say -- and I want to get feedback from the rest of the committee members -- Jay talked about the belt-and-suspenders. It sounds like if you're looking at two different tests, either two separate donations or two different segments, if it's a first-time donor, and you are including the cross-match, you have essentially got two suspenders and a belt. It seems like it's enough.

DR. JACKSON: Other opinions about the serologic versus molecular, whether that would change your response about the previous issue?

DR. STOWELL: I agree with Susan.

DR. JACKSON: Jay, is there anything you would like to ask the committee at this point?

DR. EPSTEIN: I think it has been implicit that the committee is talking about what to put on the container label. We haven’t really talked about any desire or need to differentiate tie tags from container labels. I think everybody seems to agree -- and certainly it’s logical -- that you really want integration, and the best integration is a printed label and the best printed label is one that has been computer-generated from electronically transferred data. So that’s the ideal.

Short of that, is there a separate role for the tie tag? What I’m kind of hearing is that we already allow the printed label to contain the results on the current donation. We don't actually require that it be done by two orthogonal methods or twice by different segments. Current practice is to repeat the serology with serological reagents of a different source. So that’s sort of semi-orthogonal.

Short of that -- in other words, if our standard is that you have to have done at least two tests on the current units for a first-time donor, but you don't want to put historic information on the base label unless that has been done at least on two donations, which seems to be the general sense of the committee -- is there any role for the one-time information or the unlicensed information? We heard from Mindy Goldman the practices in Canada, which

echo the practices in some other countries, where, in essence, the transfusion service gets all of the information on whatever has been done. Was it one time? Was it the current unit? Was it twice? Was it unlicensed? Was it licensed?

Do we think that our user community should get all that information? I really only heard one comment to that point. Matt was basically saying, well, I would rather you had one standard, one threshold in your label or you don't. Then you have just sort of a general discussion, which is not so clear: How about all that other information that doesn’t quite rise to testing twice on the current collection for a first-time donor or having two historic results -- perhaps one current, one historic?

What is the sense of the committee? I would like to hear a little bit of a discussion. What about all those interim results? Do we want them provided? If they are provided, are we just as comfortable with them on a base label, with all the vagaries, or do we still see a need for providing adjunctive information? FDA will have to decide whether it must be a tie tag or we allow it to be in a database or it can be on an accompanying sheet. I think we heard loudly and clearly that that’s a GMP nightmare. But at least a tie tag that’s affixed is closer to a printed label, and it’s a practice that has been used to convey

lots of other information. Sometimes you have to do it anyway, because the testing happens after you already printed the label. So tie tags aren’t going away.

But the question is, how about all this other information? Do we want the Canadian-type system, where you get it all and it’s all stratified somehow, or do we want an alternative where you really don't see that -- maybe you can ask for it and get it, but you really don't see that -- unless it has first met some predetermined standard -- a standard for accuracy, a standard for multiplicity, a standard for orthogonality, whatever else you can think of.

DR. JACKSON: Comments?

I guess, from my perspective, Jay, from the transfusion service, whether it was a one-time -- even if it was just tested once on the current donation, we would treat that and use that unit -- let’s say it’s E antigen-negative -- just like if we had units in the blood bank that hadn’t been antigen-typed, but we have to find one and we type it and we go, okay, we have one result. It’s E antigen-negative. We’re going to use it.

So I think, from the user perspective, I don't really think we would do much with all this additional information -- whether the donor had been typed five times, one time, whether it was molecular or serologic. I really

think, from the transfusion service user perspective, they are not going to treat that differently.

Other opinions?

DR. GILCHER: If I had my druthers, I would like the electronically printed label to clearly indicate that this donor had been typed on two separate occasions. I would reserve the tie tag for the first-time donor who is typed twice on two segments. Then I would know that when the electronically printed label is there, what I would like to have had occur did occur -- that is, two separate typings from two different donations. Those are my druthers.

Do you understand what I'm saying?

DR. JACKSON: So when would you require a tie tag, for what information?

DR. GILCHER: I would use the tie tag when it’s the first time -- that is, we’re doing two segments. It’s a first-time donor. We type two segments, then we use the tie tag. In other words, the computer programming doesn’t allow that to be incorporated into the algorithm.

I’m just telling you my druthers.

DR. KUEHNERT: Why?

DR. GILCHER: Because I still feel more comfortable, Matt, with knowing that this donor has been typed twice. It addresses the issue of two separate

typings, but also the donor identity. Ultimately, of course, we come back to what we spoke about before, Brooks, and that is that the cross-match is the final determinant.

DR. KUEHNERT: If it gets tested twice, I would put it on the label. I don't care how it gets tested twice. But maybe I just don't understand the technical aspects of it. It seems like a little bit of hair splitting.

DR. GILCHER: It is.

DR. KUEHNERT: The tie tag thing -- I guess I'll just argue anything to get rid of it, because I just think it sounds like a disaster waiting to happen.

From my standpoint, it seems like, if you test it twice, you put it on the label.

DR. JACKSON: So the idea would be that if it's on the label, you know that at some point either the current donation was tested twice or two different donations were tested twice.

DR. KUEHNERT: That's right.

DR. JACKSON: That's all you need to know, from a user's perspective. That's good enough for you.

DR. KUEHNERT: That's good enough.

DR. GILCHER: And I can live with that.

DR. KUEHNERT: And with the cross-match, too.

DR. JACKSON: Right.

Susan.

DR. LEITMAN: And I would like a system that every transfusion medicine director at every hospital in the country feels is adequate for the safety and optimal transfusion practice for their recipients, so they don't feel the need to discuss with their risk-mitigation people whether it’s necessary to repeat antigen typing on that unit. I would like there to be one standard of care.

I’m fine with what Matt just recommended.

DR. PIPE: Dr. Goldman showed us that somewhat complex two-by-two table. But there was no explanation of how that’s actually used by the user. So that gets printed on their labels, with the bold, underline, et cetera, but when they actually implement that and it goes out to the hospitals, are they stratifying the utilization according to whether there’s an underline or whether it’s bolded? Or, as Matt suggested, it’s on there and says it’s negative, and it just gets used? If the complexity is not adding anything to the users, then we shouldn’t have any more complexity. It should be just tested or not.

The many suggestions for what establishes reasonable testing sound good.

DR. EPSTEIN: I’m a little confused by what we’re hearing about two times testing the current collection. The current standard is that you can label the unit and use

it with one-time testing of the current. So that's ratcheting up the current standard.

The issue that's confusing me is, is it being argued that having twice tested the current collection, you can now use that as a historic result in lieu of testing the next current collection? I think most people would say no. The issue of whether you can use that unit if twice tested on the current collection -- that's moot, because you can use and label that unit now if once tested on the current unit. The real question is whether that is now a suitable historic result.

I just think we need some clarity here.

DR. KUEHNERT: If it's a first-time donor -- so it's tested twice using two different segments -- can it go on the label?

DR. EPSTEIN: Yes.

DR. KUEHNERT: The collection label.

DR. EPSTEIN: The current unit has an affixed label, what we call the container label and what has been called the base label. You can test that collection one time and label on the base label with the phenotype.

That's not the thing in question. When you're saying you are just as comfortable if it's twice tested and you sort of don't care if it's historic and two donations, you haven't clarified whether you are now saying that the

information from that twice-tested current collection can now be used as historic information for future labeling where you don't test the current collection. That’s the important question.

I would suggest that most blood bankers would be unhappy with that proposal. I’m unhappy with that proposal.

DR. KUEHNERT: To clarify my recommendation on that, that would not be considered historical, if it’s the same donation tested in two segments. You would have to test it one more time, and then it would be historical.

DR. EPSTEIN: So, you see, you actually do, then, support testing two independent donations before you permit historic labeling without current testing.

DR. KUEHNERT: Right.

DR. DIMICHELE: My understanding of the issue, to get back to Jay’s question, is it’s essentially an issue of whether the two tests represent methodological verification or donor verification and linkage or both. I had that question as well. My understanding is that both methods have a lot of concurrence, a very high level of concurrence, but one method versus the other has not yet been -- that experiment hasn’t been done.

I went back to the American Red Cross and I asked about that methodology. I understand that when they do

test a single unit twice, they do it with two technicians, two different reagents, and two segments. So methodologically those two tests are somewhat different. They are not occurring temporally at different times. The only issue is that it's on a single unit. To the extent that the two different tests really verify donor linkage, then that's not happening.

So I think it's just a matter of how we're using those two tests and what makes the blood bank, the end user, and what makes the physician who is actually giving that transfusion feel more comfortable.

I guess it comes back to the issue of donor linkage. I think we heard in some of the public comment that the blood systems do feel that their donor linkage process is well validated. But I also understand that the working group is also taking another look at that. Maybe I'm wrong. But if the working group is taking another look at that, I think that might be really, really helpful in being able to figure this out, because I think we really believe that all the information should be on the unit.

My only other point is, with advancing technology, one would hope that the information that is on the unit can be scanned and any detailed information can be obtained, such that if somebody wants more detailed information, that should be available from the barcoding.

You should be able to distinguish in a barcode two tests on the same unit versus two separate tests versus the fact that this donor may have had 16 tests or 30 tests. Probably some of the American Red Cross donors by this point have had quite a few tests. I don't know how many, but they are certainly up there -- or whether it’s by genotype or by serological phenotype.

I think that information could all go on the label. If somebody just wants to look at what the end result is, they can just look at what the end result is, and if somebody wants additional data, they can have additional data. I’m not sure that that’s mutually incompatible.

DR. JACKSON: Toby.

DR. SIMON: One point, though. I think if the current unit is being used very often, it will have been labeled and it will be removed in order to look -- for example, you may take an Rh-negative unit to look for an E-negative or something -- confirm that. There I think you have an obvious use of the tie tag, because you already have a label that doesn’t indicate the E status of that donor.

So I think you would still have a use for a tie tag, for work done on the current donation after it was originally labeled.

DR. JACKSON: Either at the blood center or at the hospital.

DR. SIMON: It could be either one, right. If you called your blood center and said you need such-and-such, rather than going to their historical database, they took ten current units and screened them, then logically that would go on a tie tag because you already have labeled the unit. Otherwise, the historical information, I think, should go on the label.

Whatever you can get into the barcode would be great. I don't know if you can get all that information in.

DR. DIMICHELE: I think that’s what Canada said they do. They said they use the tie tags if they actually need to put on more information after the original labeling.

DR. GILCHER: I think Jay hit the nail on the head when he used the word “future.” I kind of mixed that up, and I apologize for that. We’re talking about future labeling without testing. That’s really what we’re talking about -- future labeling without testing. That’s where I would want two separate donations to assure that it was the same donor and, of course, the same result. So future labeling without testing.

DR. SCHEXNEIDER: The third time that a donor

comes in, you look at his or her name and Social Security number, whatever, and say, we know that you are E-negative and we're going to label your unit as such, just by that. The first two times, you test them. The very first time the person comes in, we do it two times with two different segs. The second time they come in, 56 days later, we're going to do it again. The third time they come in, we don't have to test them for E.

That's my understanding, and I support that approach.

DR. LEITMAN: I don't think we want to set a standard for what to test the donor on the first time they are tested. That's an institutional practice. You test them using, hopefully, licensed, validated methods. From what Jay just reminded us about, if you test that unit, a segment from that unit, you can put that in the integral label. That's not what we're here to discuss. You can do that. We're not here to say you have to do that on two different segments by two different technologists. If Red Cross chooses to do that, that's fine. But we don't want to impose that standard on other blood collecting centers --

DR. JACKSON: Or hospitals.

DR. LEITMAN: Or hospitals -- any collecting facility.

What we are saying is that seeing on the base label, the container label, the phenotype could be equivalent to two things: having tested that unit or having two historical typings done on two different donations. It could mean one of two things. As a physician in the transfusion service, I would find that acceptable and I would not feel a need to repeat that.

DR. GILCHER: Would you allow future labeling without testing?

DR. LEITMAN: I just said, if there are two prior red cell antigen typings done on two different donations in the past, that would be adequate for me.

DR. JACKSON: Any other discussion about additional information by tie tag or any other thing? I thought we just heard a good reason why you might want to use that, if it’s already labeled, and provide that information.

Jay.

DR. EPSTEIN: I want to come back to the question of standards for linkage. I think what we have heard is that current practices are pretty good, but we shouldn’t forget that they are completely unstandardized. It’s voluntary what a blood center uses. Some will use Social Security numbers. Some will use name and birthday. Some will use home address. We don't have a standard.

So part of the question is, if we move toward permitting base labeling with historic information, should that be accompanied by some specific requirement or validation process for linkage of identity?

This goes beyond just the question of whether retesting separate donations is itself a cross-check against that system, because I think it is. For argument's sake, let's say you have a weak system or there's a computer glitch or whatever, and donor linkage is not well established. Retesting at least once is a safety check of the integrity of linkage. So it does serve that purpose to some extent, above and beyond the issue of just reconfirming for accuracy.

This is the same answer I gave earlier to Dr. Pipe. I think it does two things.

But I just want to get to the issue of standardization. I think we have heard that donor linkage is, generally speaking, good. I can tell you, it's far from perfect. There are errors in databases. We see them. We get BPDRs. People run Soundex programs to deal with the slight permutations of names that got spelled one way one time, another way a different time, or someone used a nickname the first time, they didn't use the nickname the second time, the birthday might have been the same for two different donors with the exact same name. All of this

happens.

I think the question of whether there should be a standard for donor linkage concurrent with allowing historic information on base labeling is material. Again, the committee can advise that there has been enough validation, things look good, the industry data are compelling, and so be it.

Alternatively, the committee could advise that things look good, but we want to know that the things we're doing should stay in place, so let's have a standard.

I'm just reminding the committee that right now there isn't one. Yes, we always expect validation. But what's actually being done isn't one thing.

DR. JACKSON: I would think that in the current systems that are used, where you find errors is where you have these duplicate donors that are identified as two different individuals, and therefore this would not really be an issue on the historical typing issue. I think it's the converse, where two different individuals are considered the same individual. How common is that? I don't know, but I would think it would be low.

You see the report. Does that happen? I could see the opposite happening quite a bit.

DR. EPSTEIN: I can't give you a number.

DR. EPSTEIN: Allene Greer is rising to the

microphone with the answer, I hope.

MS. CARR-GREER: I’m sorry, I don't have the exact answer to that. I was going to try to offer some more explanation of the reasons that blood establishments have processes in place for donor linkage and how they are used.

When donors come into the facilities and they present for blood donation, these processes begin. They must be completed before the blood product is made available for distribution. Some are requirements or recommendations and others are really facility SOPs for such things as following frequency of the donor’s visits, because they maybe are trying to track iron deficiencies and things like that. They are have to make certain that the donor is not losing too many red blood cells, if they are doing frequent plasma or platelet donations, things like that.

But most importantly, these processes came into place to ensure that the donor does not have already a deferral of record that should prevent them from donating that day. We began to pay particular attention to these issues because of HIV and hepatitis. These are critical processes that every establishment has to have.

Clearly, how the establishments identifies the donor is what makes the process work. There is no standard

from state to state or from establishment to establishment. It is what works in that community. It is defined in the establishment's SOP. As I said earlier, FDA inspections, AABB assessments look at these processes on inspection cycles, assessment cycles, to try to get a sense of the process being in control. If issues are noted, they are brought to the firm's attention.

So these processes exist. It was particularly called out at one time about the issue of duplicate donors. It's a real issue. I came from a blood center. It was a huge issue for us to sit down and go through, before we had better computerized systems, ways of detecting the donors when they presented. We spent several days once a year combing through records looking. We had several ways of looking.

So establishments pay close attention to issues like this. They are very important to them.

That's what I wanted to say. These processes are important. They are there. They are inspected and they are assessed. The workgroup looked at it. In the presentation that you heard earlier, the workgroup said that they didn't think these processes needed further validation.

DR. DIMICHELE: To your point, I'm just looking at one of the slides from Rebecca See's presentation. I

just want to split hairs for a second and make sure I understand.

It said that blood centers currently ensure donor identity throughout the donation and manufacturing processes and that establishments are inspected, FDA, and accredited, AABB, under requirements sufficient to ensure identity of donors and donations.

Are those SOPs that link a donor to a specific donation or does that also include linkage to prior donations? Do both come under the accreditation and the inspection process?

MS. CARR-GREER: The donor record includes the history of their donations, so that when the donor presents, you can look in their history and see if there's a previous issue that affects today's donation. The history is there. It is why we hear stories about packing slips containing historical information. It's there.

DR. DIMICHELE: Again just for clarification, the process is not standardized, but it is -- including linkage -- it is inspected and accredited at each collection agency.

MS. CARR-GREER: In inspections and assessments, the inspector or the assessor looks at the firm's SOPs to see how they do it at that facility.

DR. DIMICHELE: Thank you.

DR. PIPE: If I heard correctly, though, there's no current practice whereby labeled units are going out where there hasn't been any testing, like has been proposed. Currently no units go out based solely on labeling by historical testing.

MS. CARR-GREER: You're talking about face labels on the bag with historical -- I believe in the US that is not occurring.

DR. PIPE: Right. All I'm asking is, are the different agencies as comfortable with their linkage processes in an environment where they would entertain units going out without testing? You are comfortable with your processes right now, where there is still testing going on of the units, if that's being applied to the label. Are you equally confident in your linkage processes if unit testing is not going to happen?

MS. CARR-GREER: I can't answer for every establishment. I guess I would say I would expect it would be the same situation as it was for *T. cruzi*, when that was introduced, where labeling in the circular of information says that it was found negative on this donation or a previous donation, and the guidance that was issued and the conversations that occurred included the fact that your process needed to be certain that you could track -- just what we were talking about, that you had processes in place

to link the previous testing that occurred to the donor. If you couldn’t do that, then you really shouldn’t be labeling like that.

DR. JACKSON: Do you have a unique number for every donor -- you must -- that goes across, regardless of the birth date or name? There is a unique number that is associated with some demographic important information, right?

MS. CARR-GREER: That’s right.

DR. JACKSON: So the real issue here, then -- if somebody comes in initially as a donor and is E antigen-negative, and they come in again and they are under somebody else’s name, that’s not really a problem, because we are not going to consider that as being two donations, because they would be considered two separate individuals. The issue is if somebody comes in and is E antigen-negative and then somebody else comes in and is typed as E antigen-negative and is somehow assigned that first person’s unique number that identifies them as the same individual, even though they are two different individuals. Then you wouldn’t have, really, tests on two separate donations from the same individual.

That, to me, is the issue. Does that happen? I don't know.

DR. LEITMAN: There are other places where errors

can occur. The staff person labeling the tube with the label that corresponds to the unique donation number labels the wrong tube. There are all sorts of --

DR. JACKSON: Right. In other words, they are assigning the wrong unique -- that's what I'm saying -- or it's a different individual, one or the other. It's the same thing, though.

DR. LEITMAN: Those are rare events, but no one, I think, here would say that they never happen.

DR. STOWELL: I should also point out that that's the existing situation for ABO Rh and viral testing and everything else under the sun. If somebody picks up the wrong tube and mislabels it, then that error occurs. This situation is absolutely no different than any of the rest of them.

MS. CARR-GREER: The difference being, though, that if we are considering the historical labeling, those other tests would be repeated. This and potentially the *T. cruzi* test would not have been repeated. That's the situation.

But, yes, labeling the tube incorrectly at the beginning -- as Susan said, I don't think anybody could say that has never happened and will not ever happen.

DR. JACKSON: Other comments on this issue about whether there should be a standardized procedure in

general?

I don't know if you want to get that broad, Jay -- not just to this issue, but across the whole blood donation systems.

DR. STOWELL: I can understand the concerns, perhaps, about to what extent this process is standardized or not standardized. But this is an issue which is far, far bigger than having to do with historical antigen typing. I don't really think these two things should be linked.

DR. JACKSON: Other opinions?

DR. LEITMAN: We face this all the time. We’re a small transfusion service, but we’re almost 100 percent self-sufficient, so we collect our own blood. We spend an awfully long time giving donors a unique donor identity card, making it as small and slim and nice-looking as possible so that they want to keep it in their wallets. And they still don't bring it with them. We have tried the donor identity card.

We used to, a long time ago, use the last four digits of their Social Security, plus their name, plus their birth date. Then the federal government told us we couldn’t use Social Security numbers because that was private information and we couldn’t put it into our computer record.

This is a challenge that I think all different donor centers and organizations have different ways of dealing with.

DR. JACKSON: Does anyone from industry want to comment on this issue? Dr. Katz?

DR. KATZ: We spend an enormous amount of time auditing these processes. But it is true that somebody has five tubes and a blood bag and a packet of barcode labels -- the alternative would be to barcode our foreheads, I suppose, and we've met with resistance to that suggestion.

I thought the comment that this is much bigger than historical antigen was absolutely appropriate. We used to use SSN, and we were told we can't. Now we assign a unique number to every donor and hope they bring it back.

There's nobody here from Indianapolis. They are using some kind of biometric marker, iris scan. So that stuff we're working on, but it's just not there yet.

I think it's important to understand that there are current irreducible manual steps, that labeling the container and the tubes and the donor card is a manual process. We have very stringent SOPs that are designed to keep from mislabeling. It does happen. It has not happened at my former center in the past 12 months. But 24 months ago, it did. We found it because the blood type

didn’t match. It does happen, but it’s very rare. It’s more important for donor deferrals for behaviors and prior test results than it is for historical antigen.

DR. CAHILL: I was just going to say, it is a rare event, but it many times is caught on the repeat ABO Rh. We receive then a discrepancy with a historical and then we do the investigation to try to figure out how this donor now has two different ABO Rh types.

DR. JACKSON: That is picked up at the donor center as opposed to the hospital.

DR. CAHILL: Yes, it’s picked up at transfer of test results from our testing laboratories, when the computer system is verifying the ABO Rh matches.

DR. STOWELL: I was just going to point out for people who maybe aren’t involved in blood collection that most of the systems which are in place now have got automatic checkers which look for similarities in names, ID numbers, and so forth. When you put in the name of the donor, you not only get the donor’s name, but you get a bunch of names that look a lot like it -- and trying to decide if there’s reason that there could be confusion between the identity of this person who is sitting in front of you and which of your donors is on the list.

DR. KUEHNERT: With all of this, you still have the cross-match, right? No matter how much we talk about

just relying on historical typing, there’s still going to be a cross-match. That’s not going to capture all the potential for reactions or potential for alloimmunization, but it does catch most of the more severe reactions that might occur. Is that right?

DR. JACKSON: It should catch any acute hemolytic transfusion reactions. It may not prevent delayed hemolytic transfusion reaction, but it should catch the acute.

DR. SIMON: I’m kind of interpreting Jay’s comments to say, given that there isn’t a standardized method of assuring this linkage, are you still comfortable with the historical information? I’m gathering from the discussion that we are. I don't know if that answers the question.

DR. EPSTEIN: I hear you.

DR. JACKSON: Is anybody not comfortable? Put it that way.

DR. LEITMAN: Can I ask the committee a question? Someone mentioned that we didn’t ask Mindy Goldman why her two testing centers -- or she felt it was necessary to underline or not underline this unit or not this unit. One could create systems that were like that. If the current unit is tested, for whatever reason, it’s indicated an eye-readable or bar-readable format in a certain way. But if

it’s historical only on two different prior collections, the readout is different.

Does this panel feel that that transfusion service should see that distinction?

DR. DIMICHELE: I think I made a comment on that before. I think we should be at the technological stage where all that information should be readable if anybody wants it and that there be a common denominator on the label if somebody doesn’t want to look at all that information and feels perfectly comfortable with the unit being labeled as is.

But I think, in some ways, we should almost be t the technological stage where a lot of this information and the patient’s history could be readable off labels, to the extent that it’s important to be read and to be distinguished. I agree. I think that’s very important.

DR. JACKSON: But I don't think we actually need to print all that information on the label.

DR. STOWELL: I think you’re saying it should be incorporated in the ISBT or --

DR. DIMICHELE: That’s right, so that if somebody wants to go back and look at it -- particularly if there’s something that happens, and then you want to go back and look at the unit, or if you happen to be someone at a transfusion center who would like to look at that just

because you have had problems with that recipient before or whatever, and you feel like you need to go -- this is where the individual patient care issue comes in. There may be times when you may want that information, and then most times, 99 percent of the time, you don't need that information. I can imagine that would happen.

DR. STOWELL: The techno geek in me would really like to have all of that information. But the fact of the matter is, that information is still in the donor center. Even if it’s not on the label in that detail, it’s always recoverable information. So it’s not entirely necessary.

But I agree. Having a plainly printed label that just has the antigens which are negative is fine, and if there’s a method either embedded within the barcode or by going back to the donor center where you could track down the details, I think that would be adequate.

DR. JACKSON: I would agree.

Any other comments on this? Jay, anything else you want to bring up? We have a couple of minutes left.

DR. EPSTEIN: Looking at my staff to see if they are comfortable. We thank you very much for attention to the issue today.

DR. JACKSON: Thank you, everyone.

We have one quick item. Are you going to give the update? You are Lore Fields.

Agenda Item: Committee Update: Summary of October 19, 2012 FDEA Workshop on Statistical Process Controls in Blood Establishments

MS. FIELDS: Thank you. I would just like to give a quick update on a workshop that we had in October.

As most of you know, we published guidance documents recently on leukocyte reduction and apheresis quality control. Within these guidance documents, we had statistical process controls for blood and blood products. There was a lot of discussion with industry and we decided to have a workshop to discuss all these items. We did that this fall over at White Oak.

We had several goals for the workshop. We discussed the following topics:

• The evolution of statistical process control for whole blood and blood components.

• Statistical methods used for biologic product quality control.

• FDA considerations for sampling plans for blood establishments.

• Industry perspective and case studies on implementing statistical process controls.

We did this workshop via webinar and in person. It was very successful. We had 68 people who came to White Oak in person and we had greater than 124 -- we can’t

really estimate the exact number of participants via the Web because we know that in several locations there were big groups of people, but we could only actually count the facilities that were logging into the Web.

We had several presentations by FDA. Dr. Williams presented the evolution of statistical process controls for whole blood and blood components and gave a detailed discussion on where we came from, how we started developing these process control ideas, and how this really formulated within OBRR.

Dr. Scott, who is from our Office of Biostatisticians, gave a nice presentation on just general statistical process controls and CBER development of acceptable plans. He went through several plans that we have developed, both the binomial and the hypergeometric, and discussed potential other plans that industry may develop on their own and acceptable parameters that we would accept.

I gave a recommendation on our current FDA recommendations for sampling plans for blood establishments.

We also had three presentations done by industry to get industry’s perspective on how they implemented these. We decided to go with small, medium, and large blood establishments. Dr. Dumont, from Dartmouth

Hitchcock, presented for the smaller blood establishments, Mr. Collom and Mr. Negin represented the medium blood establishments, and, although Dr. Katz claimed he was small to medium-size, we did consider him a large size, and he represented his old blood center and discussed their statistical process control plans.

After, we decided to get feedback from the group to find out what worked and what didn't work, and especially how the whole webinar process came over. We had about 200 attendees that we received 50 surveys from. About 78 percent of the attendees were actually the QA/RA staff. We also had a contingent of medical directors and medical technologists.

Ninety-eight percent felt overall that the program was worthwhile -- 40 percent worthwhile, very worthwhile, 58 percent. Eighty-eight percent said the workshop met expectations.

So we felt that this was a very successful workshop and that the industry was pleased and used it as a good learning opportunity.

Some of the webcast comments: We think the new technology aided in increasing the number of attendees. We're very aware that it's expensive to fly into Washington for a one-day workshop. We think that we're being able to -- we're going to improve access to FDA and different

things that we're discussing. We will be able to get a broader audience. It also improves transparency for a greater number of the blood establishment and goals with FDA.

We had several take-home messages. Industry requested that FDA be open to considerations of alternate SPC plans. We definitely encouraged them to collaborate with each other in developing these plans and submit one plan and let us evaluate it. Then they could spread that to other colleagues within industry.

Industry also requested additional training and clarification on plans developed by FDA. We'll be working on that in the future.

FDA committed to work with industry on resolving their concerns for SPC plans and their implementation.

We have been fielding lots of phone calls and working with people on telecons to update some of their plans. There have been several things that have been identified. We hope in the future to have additional educational opportunities.

We would like to give special thanks to the sponsors of the workshop, which included CBER, AABB, America's Blood Centers, and HHS Office of the Assistant Secretary for Health.

Thank you.

DR. DIMICHELE: I have two questions. The first is, I think I know what statistical process controls are, but maybe you could just explain it in a sentence or two.

The second thing is actually related to the conferencing methodology. Did you find that this method was better to convey information? Did you get as much audience participation from those who were participating by Internet versus those who were in the room? In other words, how do you think this method works best, to convey information or is it also a very useful tool for a give-and-take?

Obviously, in the federal government we're all very interested in this, the extent to which we can actually supplant people physically coming in with these methods. The question is, does it promote as much dialogue? Was there a difference in the dialogue between those who were there and those who weren't there? Those are very interesting to me.

MS. FIELDS: I think we had decent dialogue. We had a mailbox that we opened up for the people who were not on site so they could send in their questions. We got a lot of questions. We actually ran out of time at the end and did not get an opportunity to answer all the questions and went back by email and discussed with the people whose questions did not get answered at the workshop. That

wasn't necessarily ideal because everybody didn't get to hear the answer to that, but we did end up helping everyone who was looking for it.

I think we had good back-and-forth. There were a lot of questions. There were a lot of concerns. It's something that has been going on for about five years now with the new statistical process controls. Using this webinar, I think, although it's probably not as good as having everybody in the same room together, really opened up opportunities for people to attend who would not normally be able to attend. It would just be cost-prohibitive for them to come to Washington for a one-day workshop.

DR. JACKSON: Just to follow up on that, of those who thought it was very worthwhile, was that a higher percentage of those who attended versus those who were on the webinar? Do you know?

MS. FIELDS: We did not break it out that way. We just did a SurveyMonkey, and so everyone just answered the same questions.

DR. DIMICHELE: At the FDA there's an issue. I think a lot of your participants aren't brought in. They come at their own expense. My question is, how much did it increase the cost of doing business for you at the FDA? In other words, if you had run this workshop in the usual way

versus having to set up the webinar, do you know what the increase in cost was?

MS. FIELDS: The White Oak facilities on the campus in Silver Spring already have the webinar setup in their conference room. That actually did not specifically cost CBER anything. Obviously there are costs to FDA, which runs those facilities. But as far as how much it cost CBER to run the workshop, it actually was very inexpensive. There was no cost with the room. There was no cost with the webinar. Our two sponsors, ABC and AABB, picked up the associated costs for coffee and lunch and those kinds of things.

I don't know what the phone bills were for the blood establishments.

DR. DIMICHELE: It’s a true thing. When we try to do this at the NIH, you actually have to give them a cost center. So there is certainly an RMS cost involved. That’s why I was wondering.

It’s very interesting. Thank you.

DR. JACKSON: If there are no other questions, I guess we will adjourn.

(Whereupon, at 5:40 p.m., the meeting was recessed, to reconvene at 8:00 a.m., the following day.)