WORKSHOP ON

STREAMLINING THE BLOOD DONOR HISTORY QUESTIONNAIRE

Sponsored by

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and the
American Association of Blood Banks

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Lister Hill Center

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P R O C E E D I N G S

Welcome and Opening Remarks/FDA

DR. LEE: We will go ahead and get started on time. We have a very packed agenda and we want to make sure we get all the information as fast as we can.

For our opening remarks, we will hear from Dr. Epstein and as far as this topic of donor history questionnaire is concerned, Dr. Epstein might as well be the commissioner of the FDA. So, I think we have the right person to start us off on the overall framework of what we are aiming towards in terms of streamlining the donor questionnaire.

Dr. Epstein.

DR. EPSTEIN: Thank you, Jong, and my thanks to those at FDA and AABB who organized this workshop.

Good morning, everyone, and welcome to Washington on a nice fall day, which you are about to spend indoors.

We are here today to discuss streamlining the blood donor history questionnaire. I think it is always valuable to put things in context. This is one of a set of initiatives under FDA's Blood Action Plan, which some

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of you may recall was initiated in July '97 to address a whole series of issues relating to the blood supply and FDA regulation, and, in particular, in approximately November '99, we added an issue area of monitoring and increasing the blood supply in recognition of the fact that we had entered a period of critical blood shortages and also that we had put in place a series of policies which had the impact of we hope improving safety, but also of straining the blood system, for example, the CJD-related deferrals including exclusion for traveler residence to the UK.

So, there were five areas under that action item. They included monitoring the blood supply, and as you know, the NHLBI developed contract funding which went to the AABB's NBDRC, which has been in place to monitor supply data retrospectively as far back as October '99, and then prospectively since about January of this year.

A second issue area has been to encourage more donations by eligible donors, and toward that end, FDA has developed a draft update on donor incentives which will soon issue as a compliance policy guide, and a preliminary planning workshop was held in February of

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2000 which has led to some subsequent activities along the lines of trying to develop pilot programs.

A third area is improving donor relations as part of recruitment and retention. This somewhat crosscuts the current topic which bridges both the area of scientific issues related to donor restrictions, as well as perhaps some of the user friendliness issues that affect donor relations.

So, therefore, we sponsored a workshop this last July on Best Practices in Donor Recruitment, and we are also in the process of developing guidance on the computer assisted, self-administered interview, as well as ultimately, also further guidance on abbreviated questionnaires, which should build on the work products of this meeting.

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It is under this umbrella that we are also working on the initiative to simplify the donor questionnaire. We also have had an initiative to remove restrictions to safe donation, in particular, the issue of permitting donations by persons with hereditary hemochromatosis came to the fore as a potentially

valuable source of blood donations and the issues of safety related to removing an undue incentive related to indirect remuneration has been addressed, and we have a stated policy to grant variances or exceptions to the regulations to waive the requirement for a week intervals and for labeling the disease state for medical phlebotomy.

We have already been approving such variances when supported by appropriate data, and we are moving forward with a guidance which we hope will issue soon and ultimately a change to the regulations.

Additionally, we have had a series of scientific workshops to reexamine the basis of current donor deferrals. In particular, there was a workshop at the Centers for Disease Control this last June to look at issues mainly related to updating the current PHS guidance on HIV donor suitability criteria, but also other conditions, and we have had both workshops and Blood Products Advisory Committee to look at such things as the exclusion for history of male sex with males, the antibody test for syphilis, the current testing for p24 antigen for HIV-1, et cetera.

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Lastly, we have been pursuing with the help of the Department ways to address the economic issues that are being faced by the blood industry. So, this is the general context in which we have been operating.

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So, today's meeting is on the issue of streamlining the questionnaire, and basically, what we are talking about are impacts in three areas: donor selection as it impacts blood safety and as it impacts blood availability.

So, perhaps it is worth a moment just to define terms, what do we mean by "product safety." Well, safety is not absolute, and I think probably the most useful definition of this, a quote from Jane Henney at a talk that she gave in February of last year, namely, "To FDA, a product is safe if it has a favorable ratio of benefits to risks when used for defined indications in specific populations." So, it is a very context-dependent notion.

In that regard, I would say that zero risk, while, of course, it is an ideal goal, cannot be construed as a practical mandate, that we do accept a

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degree of risk as appropriate to context although, of course, we try to minimize risk.

Now, "product availability," I don't know that it has a standard accepted definition, so I have simply created one, which is the assurance of timely access to appropriate high quality products to meet patient needs, in other words, the right product meeting the right quality is there when you need it for a purpose.

"Donor selection" is the first step towards assuring product safety and availability for blood and blood components. I think we all understand that, and I won't belabor the process because there will be much discussion of what that is.

So, the challenge to us and the blood community is to devise a donor selection process which optimizes both blood safety and blood availability.

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So, now, in this context, what exactly is the role of donor selection, and there are a few things I think worth noting because they have different dimensions in terms of how they might be approached.

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First, when we utilize the donor history question and also donor education, which antecedes it, of course, we exclude donations and we try to capture donations which present risk for transmitting infectious diseases. Some of these are things for which we have tests, too, so why also select by screening?

Well, the answer is because it reduces the amount of conditions that the tests have to track, and I am sure we will hear numbers later, but the effectiveness of these donor exclusions is around the 92-98 percent range for different conditions or essentially a 1 to 2 log reduction.

What that means is that if we weren't doing it, we would have 10-fold to 100-fold more positives to catch by testing, which could really stress the testing system. So, one benefit that we have is it reduces the demand or the pressure on the test system.

Now, one could, of course, argue the other side of the coin, which is testing is very good, that it essentially picks up everything to be found, so why not just rely on it, but then there are two other very, very important concepts, which is that screening also enables

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us to exclude window period cases, in other words, cases where the donor or prospective donor has become infected, is infectious, but has not yet manifested a detectable marker at least by available screen technology. So, that is an independent safeguard compared with testing per se, and you can see that the two must work hand in hand.

Additionally, screening is helpful to improve safety for diseases or conditions for which there are no tests. I think that is self-evident, and also it gets you back to the history of why we have in many cases screens and tests, because screens were implemented before tests were feasible, usually when a condition was described, when it was known transfusion transmitted, but before we had identification of an agent or an available screening test technology.

Then, lastly, perhaps a neglected point is that even though we may effectively identify the vast majority of contaminated units by testing, there is a problem when you collect infectious units because there is a period of time when they exist in the inventory, presumably in quarantine pending a determination of suitability, but before testing and before they are actually physically

interdicted, and during that period, there is always the possibility of release through error.

In fact, release through error may be the dominant form of release of infectious units. This may vary depending on the context where blood is collected, the system is in place, whether they are manual or automated, and other factors.

But the bottom line is that this is a risk, it has been measured in some studies, particularly by Jeanne Linden, and that we do periodically get reports of known positive units that were released through error.

So, having exclusions up-front that significantly reduce the number of potentially infectious units collected in the first place, also adds to blood safety.

Related to that is worker protection. Again, the fewer units that the staff have to handle that are potentially infectious, the safer is the work environment.

So, these are the drivers for maintaining and indeed perfecting donor selection, but there is a balance as I have been alluding to.

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On the one hand, excluding donors contributes to blood safety by preventing disease transmission, as I explained on the previous slide, but on the other hand, there is a down side, which is that the methods of exclusion do discourage volunteer donation, they make the process less pleasant, it is cumbersome, it is burdensome, it does add to time. We have questions whether we maintain valid screening when we keep asking the same questions over and over and over again of repeat donors.

Also, we give people negative medical messages when we tell them they are excluded, perhaps for reasons that are not always clearly understood or explained, and then, in addition, because these technologies are nonspecific, they capture a small percent of risk conditions at the expense of a large number of donor exclusions, we waste a lot of the potential donor base, resulting in unnecessary deferral and some compromise to blood availability, so, of course, the idea is to try to strike it right.

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So, the goal is to see if there are ways to modify the existing donor selection process in order to optimize donor protection, by which I mean eliminating all of these secondary phenomena that have negative impacts on donors and their willingness to donate and the sense of their health, that contribute to blood safety based on well-established scientific principles, so that we know that the exclusion is doing something meaningful by way of safety protection, and finally, that optimized blood availability by minimizing the amount of wastage through needless exclusion.

So, what are some of the issues that we will be considering in the workshop? I have tried to organize these hierarchically, kind of as a logical progression, you know, of how you must think things through.

First, we need a strong scientific foundation. We need to understand the basis for the deferral criteria.

We need to consider then validation of the screening questions as a process. This, of course, is closer to the focus of today's workshop.

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We need then to examine what the sensitivity and specificity are of the methods that are put in place. This is sort of moving toward measures of utility.

Related to that is understanding the predictive value of screening. That, of course, is context-dependent because it depends, not only on the sensitivity and specificity, but on the prevalence of the condition in the population, the positive predictive value being the proportion of positive answers that are accurate or true.

We need to understand the impact of the screen on disease prevention in recipients, not merely detection of a condition, but also considering the risk of transmission and the disease impact if there is transmission.

We need to ask whether there are alternative available and sufficient test technologies or, putting it another way, what is the right interplay between the screen and the test, and lastly, we need to consider, as a collective in the PHS context, costs that may be associated both with screening and with testing on the model of trying to have efficiency in the public health.

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[Slide.]

Now, this is another outline of again a paradigm to consider the business of the day. We try to progress from identification of risk factors, to then having effectively worded questions which are validated. The notion is that this should then evolve into what I have called the "standard donor selection process," and one of the regulatory questions is should we mandate that.

Right now we don't. Right now we will consider ad hoc donor questions or history questionnaires developed site by site, and we will review them for licensees, and they may not be worded the same way. Of course, they have to cover the same ground consistent with regulations and guidance, but they don't have to use the same words or the same formats.

One question that can legitimately be asked is how can we ever ask how these things are working if they are not standardized as instruments and we are dealing with, you know, diverse questions and diverse formats, what exactly do we measure when we try to measure impact.

So, the question then is should be have a standard process, and then there will be modifications to

it. Certainly, one modification, which I suppose could be a standard modification, is that of the abbreviated questionnaire for the repeat donor. Another modification is fundamental changes in format, such as the use of the computer-assisted interview or other media-driven interactions.

Lastly, there is the issue of should there be locally adapted questionnaires for conditions that are prevalent in a region, but not nationally.

Of course, all these things go on. It is just that they are not going on in any organized way right now.

Finally, we end up with a donor deferral, and we have the question which is perennially debated, whether there should be a national registry of deferred donors, and perhaps flipping the coin, should there be national registries of qualified donors.

We have always shied away from this over issues of confidentiality and feasibility, who would maintain these databases, how would they be updated, how would we ensure integrity, who could access them, what level of information should be in them. So, we have never

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mandated these strategies, however, I think it still merits some thought if we get that far down this chain.

So, that is my stab at providing you with a bit of an overview, and I think that we are going to have, just scanning the program, a very productive meeting today, and I just wish to thank everyone for coming here to contribute.

Thank you very much.

DR. LEE: Thank you, Dr. Epstein. That was quite a bit more than a few opening remarks. I hope we can fulfill the challenges that Dr. Epstein has raised in the last 10 minutes or so.

Before we move on to our next speaker, I would like to just go over a few housekeeping announcements. I am told that this is mandatory in terms of our use of the auditorium. No food or beverage allowed in the auditorium, number one. Number two, message desk phone number. For messages, the phone number is 301-496-4062. Housekeeping rule number three, pay phones are located behind the visitor center. Number four, to activate audience microphone, press the mike button. That might be very important towards the latter part of the day.

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Presenters, please check in the preparation room. That doesn't quite apply here.

Anyway, having fulfilled my obligations of reading the housekeeping rules, we will move on to our next speaker. Our next speaker is Dr. Joy Fridey. Dr. Joy Fridey served as the senior vice president of Medical Affairs and is a member of the Executive Management Team in the organization. She oversees the research and development, clinical trials development, the stem cell program, quality assurance, and donor notification. She has been active in the AABB Standards Committee since 1995, focusing primarily on blood donor qualification and the donor history questionnaire. She is currently the chair of the AABB-sponsored multi-agency task force to modify the donor screening questionnaire.

Dr. Fridey will now give us her opening remarks from the AABB standpoint.

The Blood Donor Questionnaire:

A Roadmap to Change

DR. FRIDEY: While Mr. Wilczek is locating my talk, I would just like to make a few comments. First, I would like to thank the FDA for the opportunity to

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collaborate on this workshop. It pertains to a topic that is of concern and interest to all of us, and the AABB appreciates that we have had this chance to do this together.

I also would like to thank specifically the people who have spent so much time pulling this together, specifically, Joe Wilczek from the FDA and Kay Gregory from the AABB. They have spent a huge amount of time in pulling this together.

[Slide.]

What I would like to cover today is to give you a brief historical overview of how we came to this point. I thought a little walk from memory lane might be helpful and appropriate, spend a little time talking about the current state of affairs in terms of the donor history questionnaire, and then talk about the task force plan for change.

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Well, 1953 was the beginning. This is the year that the American Association of Blood Banks' Manual on Technical Methods and Procedures, as it was then called, we call it the Technical Manual now, first recommended

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that a donor record card, as they called it, be implemented, and in addition to a number of demographic items about the donor, it enumerated some 21 medical and social items about which the donor needed to be asked.

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I have these listed here for you. We won't go through all of them, but some that are of interest would include tuberculosis, brucellosis. These were both dropped in 1974. Donors were asked about allergic states. If someone had asthma, they were permanently deferred. If they were in the middle of an active allergic state, such as hay fever or food sensitivities, they were deferred for that donation, but there were a number of other things, some of which we still ask about today, for instance, history of previous transfusions, history of previous blood donations, pregnancy.

Now, you will notice that some of these items have asterisks next to them, convulsions, diabetes, drug addiction, inoculations, vaccinations, et cetera. In the 1962 version of the AABB Technical Manual, for all intents and purposes is what I will call it, these items could be eliminated in the questionnaire.

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The goal here was to make the screening process as fast as possible in times of national emergency when you really had to get blood out the door quickly. I scratched my head trying to think what was going on in 1962 that some questions would be eliminated to speed up the screening process.

Does anybody in the audience care to help out? Cuban missile crisis, Bay of Pigs. It was kind of an interesting little twist.

[Slide.]

Now, what I thought would be fun to do is just quickly go over some items of interest that are now kind of anachronistic and curiosities. Plasma donors, for instance, were not supposed to eat a fatty meal before they came in to donate, and the Technical Manual made dietary recommendations. They could eat bread or toast without butter, coffee or tea with sugar, but without cream or milk. These are actually very good dietary recommendations that if we all followed today, we would be, probably many of us, a lot thinner.

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There were actual deferral periods. People who operated cranes, heavy equipment, drove buses, taxis, trains, engaged in scuba diving, sky diving, worked on ladders, scaffolding couldn't donate if they were going to go back to those activities within 12 hours. Flight crews were deferred for 72 hours where they were not taken if they were going to fly in 72 hours.

[Slide.]

Now, this one really caught my interest. In 1962, the Manual said, "Persons suspected of being drug addicts are not acceptable as they cannot be relied upon to give honest answers to questions." Not a little judgmental, however, this was changed in the next version, and a very valid scientific reason was given for deferring these people, that is, the risk of transmitting hepatitis. Of course, now we know there are other concerns, as well.

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Then, some other curiosities. In 1962, phlebotomy was described as a, quote "minor surgical procedure" and, quote "no chances were to be taken with the donor or the recipient's health." A whole blood

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donation in '62, you could only donate five times a year. That was increased to eight times a year.

There were age limits, of course. If you were over 59 in 1953, sorry, you know, we couldn't take your blood, and that was raised to 65, and, of course, now we know we are taking donors well into their 80s if they have been repeat donors and can get annual documentation from their doctor that it is safe for them to donate blood.

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Well, these are all interesting. Some of them are kind of funny, but the framers of the first donor deferral questionnaires, if you will, also had some pearls of wisdom to impart.

One of these is in the very first version, 1953, it was said that "Surroundings conducive to confidential and truthful replies to questions must be provided." They understood back then the importance of allowing the donor to be in an environment where the donor could be honest.

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In 1962, it was further said that, "The questions must be asked in non-medical terms." Very good advice.

In 1966, it went to say that, "The questions must be asked slowly and clearly, in non-medical terms, an occasional pause to give the donor time to think is recommended."

These, I think are good pieces of advice and are still relevant today.

[Slide.]

What I would like to do now is just give you a quick chronology of how events with a card developed. Now, I am not going to be all-inclusive, I am just going to hit the highlights. I am not going to talk about donor demographics.

The top line are those contributions by the AABB, the bottom line are those by the FDA. The first thing that happens we talked about is the donor history, donor record card of 1953. The next thing was in the early sixties, there was the option to eliminate some questions in the event of national emergency.

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Then, curiously, in 1966 or '67, it was specifically stated that the donor answers had to be documented. Now, presumably, they were being documented all along, but this specified that it was important to actually write down what the donor said.

Then, in 1970, meds were added, and there was a fairly extensive list of medications that warranted deferrals, such as cardiac drugs, insulin, antibiotics, steroids. If anybody was on those, they were deferred.

Then, in 1974, the AABB shifted from having an itemized list of single succinct questions--and they really weren't questions, they were items that the donor had to say yes or no to--to a series of full sentence, standard English questions that included noun and verb, and this was the origin of the questionnaire as we now know it today, and then donors were also asked to provide some kind of I.D. like a Social Security card or a driver's license.

Now, all along donors had been asked about syphilis, but in the late seventies, the AABB felt apparently that syphilis did not pose a risk. We were certainly testing for it, and in that edition, did not

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include syphilis as a question that had to be asked of donors, that is, if they had a positive test or if they have had a history of syphilis.

Cancer was added in the early eighties. 1985 was a seminal year. This is the year that we began to ask about AIDS symptoms, and we weren't asking about behaviors then, we were still using words like homosexual and bisexual in the card, which of course became problematic because when you use labels, some people that the label doesn't apply to them, but that was an important change.

In the late 1980s, the growth hormone deferral, the CJD. A memo from the FDA was sent out, and so we added a question asking people if they had ever been injected with human pituitary growth hormone, and then in 1990, the AABB actually recommended that donors be asked the HIV risk questions orally, and the concept of the confidential unit exclusion, the process by which the donor could indicate at the time of donation that although they were going to go ahead and donate, that their blood should not be used subsequently for transfusion.

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Then, we had a flurry of documents and many changes. The syphilis and gonorrhea questions were added back in on the basis of an FDA memorandum. April '92 was the very famous memorandum on decreasing the risk of transmission of HIV through blood, which added a number of formal questions that focused more on behavior as opposed to risk groups.

As a result of the fact that we had now accumulated a number of items and questions, the questionnaire was starting to get a little jammed up, if you know what I mean, and the Blood Centers of California stated work on a process to make the card a little more organized, a little more logical, and submitted that to the AABB.

The AABB picked up that project and as a result, in 1992, we had the first uniform donor history questionnaire. The FDA then added some medications, Tegison, Accutane, and Proscar. There were some malaria items that were added in '95. The incarceration requirement, if someone had been in jail more than 72 hours in the past 12 months, they had to be deferred for a year.

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Then, there were some additional CJD items added a little later having to do with whether the donor had had a dura mater transplant or had a family history of CJD.

The HIV-1, Group O geographic exclusion questions were added shortly after 1995, and there were some additional refinements of the CJD questions. In 1998, again, because the card was getting congested, newly required questions were just kind of being added at the end of the questionnaire. The AABB tried to group things more logically, like they put all the medications together, for example, they did some things with the HIV questions to make them more readable.

Then, last of all, we had more recently the CJD travel or new variant CDD travel questions, and bovine insulin question, that was added.

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Now, there are several ways to enumerate or to count the number of items or questions that we are asking donors. You can talk in terms of how many numbered questions there are on the questionnaire. Right now that number is 32, or you could talk about the number of

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question that are actually on there if you include the subparts of each question, and that number right now is 46.

But what we are really trying to get from the donor is information about specific items, and those items are incorporated in a number of questions. When you look at what has happened over time in terms of the number of items that are on that questionnaire, this is what the graph looks like.

I apologize for how this looks on your handout. Over on the lefthand side are the number of items going from zero up to 80. On the x axis are the years going from 53 up to 2,000, and you can appreciate that over time, the number of items that we have been asking donors has increased pretty dramatically as we have recognized that as we have recognized new risks and also potential risks.

Now, this pink line over here on the righthand side of the graph is the number of numbered questions which has been running around 32 for the past eight years. As I mentioned, the questionnaire right now has 46 questions if you include the subparts, but if you

consider that we are asking about 70 items and we have 46 questions on there, you are talking about a number of compound questions and multi-item questions, and I will talk about those in a little more detail n a minute.

[Slide.]

The AABB is the source of some 20 of these items. This includes questions that are not required by the FDA or standards, or questions that are required by standards, again, not the FDA, or questions based on FDA documents that don't really specifically require a question, but that AABB felt that the best approach would be to ask a question, and then there are 50 FDA items.

[Slide.]

Now, I am not a linguist, so I may not be the best person to linguistically analyze the card, but I did a crude overview of the current questionnaire. There are right now 24 single-item questions. The purpose of these questions is to get at one basic thought, one basic idea.

There are 14 compound questions, and I define these as questions in which there are two sentences basically. You could easily separate the question into two full sentences, there are two different verbs, and

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there are eight multi-items questions. Let me give you some examples of these.

[Slide.]

This is a multi-item question. It has four items. Have you ever had yellow jaundice, liver disease, viral hepatitis or a positive test for hepatitis?

[Slide.]

A compound, multi-item question is Question No. 19 on the AABB uniform donor history questionnaire. In the past 12 months, have you had a tattoo applied, ear or skin piercing, acupuncture, accidental needle stick, or--a new sentence--come into contact with someone else's blood? So, a pretty comprehensive question.

[Slide.]

Then, there are several what I consider just plain old complex questions, trying to get at maybe one thought, but there is a lot of information in the question.

Question No. 25 in the AABB uniform questionnaire. Female Donors: In the past 12 months, have you had sex with a male who has had sex, even once, since 1977 with another male? Very complicated wording.

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[Slide.]

Another complex question. Do you understand that if you have the AIDS virus, you can give it to someone else even though you may feel well and have a negative AIDS test?

We all know what this means. The average donor on the street, this may be a little bit difficult to understand.

[Slide.]

So, where does this bring us? Well, just kind of this silly little cartoon. Here, we have this big, fat, bloated thing, donor questionnaire, and we are all sort of gagging and choking on it, donor blood centers, the FDA isn't happy with it.

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What is heard on the street is this wish list from FDA's constituents. You have all heard this. Blood Centers of California hears this constantly from its membership, that people would like a short questionnaire for all donors. They would like an abbreviated questionnaire for repeat donors.

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They like questions that are easy to understand and, if possible, less intrusive. Many donors do object to the personal nature of the questions. Less repetition. There are a number of questions that have to be--well, first of all, many donors will answer all the questions, they will self-administer, but then many of those questions have to be repeated orally, namely, the HIV questions.

So, what we are getting from this is that people would favor a self-administered questionnaire. One concern that has been voice again and again is that with the exception perhaps of the questions that were required in the April '92 FDA memorandum for reducing HIV risk, there really has not been any kind of validation of questions as they have been issued by the AABB or the FDA.

[Slide.]

Attempts to cope. We have already talked about the uniform donor history questionnaire in 1992, but as more questions were added, we handled things by making them multi-item and compound questions.

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There was an attempt to reorganize the card in '98. By the end of '99, the FDA had actually approved several abbreviated versions for repeat donors, and was continuing to get proposals, when, in early 2000, it came to the AABB and asked that a multi-agency task force, with the support and sponsorship of the AABB, be put together, and that has been done.

[Slide.]

The task force charges are these, I have just worded these very simply: To re-evaluate the scientific bases of the infectious disease and other questions; to modify the wording to appropriate comprehension levels, and to do some housekeeping, group similar questions, do some reformatting when appropriate; to evaluate and recommend methods for administering the questionnaire. Here, we are talking about screening process, and this is every bit as important as making changes to the questionnaire itself. We will be hearing about ways to do that. Submit proposed new questionnaires to the FDA.

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The members of this task force include the American Association of Blood Banks, and there are

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representatives from each organization on this. The American Blood Resources Association, the American Red Cross, America's Blood Centers, Centers for Disease Control and Prevention, Department of Defense, Food and Drug Administration, National Heart, Lung, and Blood Institute.

We have an ethicist on there who is the public member of the AABB Standards Committee, and a statistician. We are shortly going to add someone with linguistic expertise and probably somebody with IT or experience with computerized systems, and we will add, as necessary, to the task force.

[Slide.]

Now, the expectation that was initially communicated to us from the FDA is that major research initiatives were not expected, that perhaps some focus groups and pilot studies should be done, but that we were not expected to launch into a REDS type of project to do this.

No research funds are available right now from FDA, and there will be heavy reliance on participation of blood centers around the country and also the task force

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members, who of course are volunteering their time and their talents for this.

We are working primarily through conference calls, we have already had a number of them, and through electronic mail. This proposal is due in 2001.

The basic message is here, there is not a lot of money to do this, and we have until sometime in 2001 to get this together.

[Slide.]

Now, this schematic just sort of shows the roadmap. As I mentioned, we have already had a number of conference calls with the whole task force for subcommittees, many, many e-mails. If I got a dollar for every e-mail I got about this project, I would be really racking up the dollars. But we have already started in this process.

In August, a survey went out to some 35 AABB members to solicit information about problematic donor questions meaning questions that appear difficult for the donor to understand, questions that are associated with subsequent callbacks, questions that the donors find

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objectionable. We also asked for suggestions on wording and other things

We also had approached the FDA about providing us with error and accident report information pertaining to screening errors, and a summary of the American Institute of Research, a project that was done several years ago, and we also asked the FDA to provide us with some guidelines in terms of which items, how we should handle the FDA items.

The information we have now received subsequently is that none of the items or questions can be eliminated, they could be reworded, some of the questions can be grouped.

So, then given that information, we are going to look at all of the questions, and we are going to do it with an eye for eliminating, when possible, and since we can't eliminate any FDA items, we will be looking very hard at some of the AABB ones to reword, combine when necessary, to reorganize the card.

A couple of side issues that we will at least talk about. Deferral periods, the FDA has indicated that

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there might be some wiggle room on deferral periods for things like tattoos or body piercings, complex deferrals.

The malaria issue is a real tough one. As you know, geography is complicated. More people are traveling. They don't know really if they have been in a malarial area of not. We do get some feedback that the health information for international travel is a very difficult manual to use although it is full of information, and we appreciate the help that that is intended to offer, but we will at least be talking a little bit about that.

Then, we will design and perform research. We will be looking for the ability of donors to comprehend newly worded questions and try to determine what we can do in terms of calculating the effectiveness vis-a-vis safety on the changes we make.

We will review the data that we collect, probably do some reworking in here, and then submit proposals to the FDA for a full-length questionnaire, and then for an abbreviated version of repeat donors, expect there will be some discussion and rework in here, and then at some point implementation

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[Slide.]

Now, there will be challenges associated with this. One of the major ones I see is communication between organizations and within organizations.

I would make a special appeal to the FDA on a couple of points. One is that the representation on the task force reflect the official FDA position for all matters for which we require input, and that the FDA provide advice and consent throughout the whole process, so that we don't end up going down a blind alley if, for example, a particular validation research project may not meet set criteria or if the FDA expectation, we would need to know about that.

I think managing expectations of the end users, the donors, and the blood centers will be very important. We are not going to produce a questionnaire with 10 items or 10 questions on it, it is just impossible. The data that we may collect may take us off in a different direction perhaps than would have originally been hoped for.

Given the parameters that we will be working within, basically, at this point in time, no or few

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research dollars with a tight time frame we will be able to do. We have to be realistic about that.

Validating within the parameters, we have already kind of talked about this.

Change is difficult. We will be looking at the scientific data that underscores each of the questions, and when it appears that the scientific data no longer support a question, then, I think everyone needs to have an open mind about whether or not that question or item should be eliminated.

[Slide.]

The last thing is competing priorities. Everybody wants brevity, but how can you have brevity when there is so much information that we have to ask of donors. Brevity versus comprehension.

Alan Williams and Sharyn Orton published a paper in Transfusion recently showing that a group of people who were eligible to donate blood were asked about five specific questions. This was in a focus group format.

They looked at these questions and said, boy, these are tough, we can't understand these, these need to be broken up. As a result of that focus group, based on

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those five questions alone, there would have been a net addition of three questions to the questionnaire in order to make things simpler for the donor to understand, so the issue of comprehension versus brevity.

Then, there is the whole issue of speed versus efficiency. I mean we want to be able to move the donor through the process quickly. We feel that donors are owed an expedited and efficient process, and we don't want to dampen their enthusiasm because the process takes so long, because the questionnaire is so long, but yet we also want to strive for accuracy.

[Slide.]

So, having provided that context, I think that what we will be able to produce is an easier to understand what I call "full-length" questionnaire, this is for people who are not repeat donors, and hopefully, a simplified format, some questions and items may be eliminated.

An abbreviated questionnaire for repeat donors, and last, recommendations for streamlining the screening process, which I have said is extremely important, is

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important as trying to make the questionnaire more usable.

[Slide.]

So, hopefully, this is where we will end up, with a slightly reduced donor questionnaire, hopefully, we contain the beast a little bit.

That concludes my presentation. I would like to thank you for your kind attention.

[Applause.]

DR. LEE: Thank you, Dr. Fridey, for that wonderful thorough presentation. I feel like I know what I am talking about now when we talk about streamlining the donor questionnaire and what we are doing as a task force.

Our next speaker is Dr. Andrew Dayton. I think you are very familiar with Dr. Dayton. He has the dubious distinction of tackling this very complex problem every time it arises from the Agency's standpoint. He had done a wonderful job at the last BPAC, and he is asked to repeat his performance for our benefit this morning.

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Dr. Dayton from the Division of Transfusion-Transmitted Diseases of FDA.

FDA OVERVIEW ON CHANGING

THE DONOR QUESTIONNAIRE

FDA Decision Making Process for

Adding/Modifying Questions

DR. DAYTON: Thank you.

[Slide.]

I have been asked to talk on FDA's approach to developing donor deferral questions. I think you will find that it is not terribly surprising to you what I am going to say.

I have listed here the basic steps in the process of developing donor questions. Just to read through this, first, we identify the risk factors. Once we have done that, we attempt to formulate questions, then, we try to seek consensus, and, of course, we will go back forth between seeking consensus and formulation questions.

Subsequently, in the ideal state, there is a process of validating questions, but I will talk more

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about that in a minute. Finally, there is implementation.

Ever step that I have listed here is fraught with peril, and we, as an agency involved with protecting the public health and basically having been given a mission of zero error tolerance mandated by Congress and public opinion, we feel that we have to be very conservative, and there is good reason for that.

I don't need to tell you how easy it is to transmit certain agents by blood, and the whole system is just waiting to transmit a dangerous pathogen, such as has happened with HIV. So, the point is that errors are disastrous, and this requires us to adopt a conservative approach.

In identifying risk factors, often it is very difficult because we see something, an emerging problem, very early on and often the policy is required to precede the data. In fact, this can even be the case for issues which have around for quite a while.

To bring up a very recent issue, what we just took through BPAC, we reexamined the deferral of male homosexuals, and what it came down to I think was really

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trying to identify a group that might be allowed to donate if we changed the policy, but then we didn't really have data on the prevalence and incidence of HIV in that particular subset of male homosexuals.

So, even for a disease which has been with us for 20 years, and behavioral patterns which have been with us forever, there still isn't the data we really need to make a final decision. So, very often the policy precedes data and this always runs the risk for getting us into difficult situations.

[Slide.]

Now, once we have identified the risk factors with the caveats I mentioned, then, there is the process of formulating the questions. This is really no surprise. What we do here is have internal discussions. We try to capture the risk behavior as best we can.

We pass this back and forth. It goes through all levels of the office. The point I want to make about the wording, when I say here the exact wording is not critical, that doesn't mean that we don't think the wording of the question is critical, we realize that very often the wording of the question is critical, but, in

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general, when the FDA makes a recommendation for a question, we are not expecting that question to be asked verbatim in the questionnaire.

We freely recognize that there may be situation-specific or industry-specific preferences for doing things in a certain way, and we welcome advice from the industry and appropriate modifications.

[Slide.]

Now, to seek consensus on this or basically public support, we have several approaches. Typically, we will make a proposal to the Blood Products Advisory Committee. All of you have seen this happen, or sometimes we will propose language in draft guidance documents. Typical of this would be xenotransplantation. We will discuss issues associated with these questions in workshops.

Very often we will take the recommendations and go back to step 2, which is reformulating the questions. Several times there will be several cycles going back and forth, requiring discussions and input from a number of different directions.

[Slide.]

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Now, the process of validation is somewhat controversial. We are always asked to validate, and it how well these questions work, and it is a totally correct request. In general, we haven't had the resources to do validation. We have strongly encourage the industry sector to help us validate questions, particularly because there are all these blood collections going on, and since the system is largely set up for having people come in and be asked questions, it is a prime opportunity for trying out new questions.

But again, this goes back largely to the point I mentioned in the beginning about policy often preceding data, again, we are often faced with a public health crisis looming. We don't really know the exact numbers or how to put a quantitative estimate on the risk, so we very often have to go ahead and get these questions out there, and then there becomes a sort of retrospective validation where we do sort of find out how these questions work, and they can be modified afterwards.

[Slide.]

Again, this is largely an issue of timing, the question being if we are faced with a looming problem, we

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have to get something out, it is better to get something out that works reasonably well quickly rather than something that is perfect but late.

[Slide.]

Finally, the implementation at the end pretty much speaks for itself. We will usually release that as either a guidance document or a memo to blood establishments.

So, just to summarize, there are no particular surprises here. I think most of you have seen all of this in action. You and we realize that the system is not perfect, and we feel that we have done a reasonably good job with what we have had to deal with, but we know that we can do a better one and we are very happy for task forces such as this to contribute to the process.

[Applause.]

DR. LEE: Thank you, Dr. Dayton.

As Dr. Dayton stated, there were no big surprises in his presentation, however, that whole area has been somewhat of a black box to many people, particularly those outside the agency, but in some cases to those inside the agency, as well, so it was very nice

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to hear from Dr. Dayton a clear crystallization of what we do in the public process.

We will now turn our attention to error and accident reporting, and we will hear from Sharon O'Callaghan, who is currently with the Office of Compliance and Biologic Quality, and who has dealt with the subject matter for a very long time and has often supported everyone in OBRR in pulling data about errors and accident reports.

Ms. O'Callaghan.

Error and Accident Reports/Post Donation Information Impacting on Donor History Questions

MS. O'CALLAGHAN: Thank you, Jong. It is a pleasure to be here and always a pleasure to talk about errors and accidents, one of my favorite subjects.

[Slide.]

I was asked to present some of the data that we have compiled from the Error and Accident Reporting System specifically referring to the donor suitability issues. What I am going to cover this morning is related to the post-donation information reports, as well as error and accidents that occur in donor screening.

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To give you an idea first to identify how many reports that we receive and who has been submitting the reports, for FY 1999 we received over 15,000 reports; for FY 2000, for the first three quarters, it is a little over 16,000. We probably will end up with about 22- to 25,000 for FY 2000.

Licensed blood banks and plasma centers are currently required to report, so they are submitting the bulk of the reports. Unlicensed blood bank have been requested to voluntarily report from a memo we issued in '91, and we have received some reports, but not a lot, from them.

[Slide.]

Post-donation information is information that is provided to the blood center either at a subsequent donation or shortly after a donation, that had that information been known at the time of donation, would have caused that donor to be deferred.

I know that is a long explanation of post-donation information, but basically, it is when the donor comes in and answers all of the history questions

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appropriately, says no to all the high-risk behaviors, comes back the next time, eight weeks later, maybe even longer, and now all of a sudden gives information that they had a tattoo or they had ear piercing, some type of high-risk behavior within the period of that previous donation, would have caused them to be deferred, so that is going to affect their previously collected donation.

The post-donation information is either provided by the donor himself, it can also be provided by a third party. We have had reports come in where the police station notifies the blood center that they just arrested somebody. These are one several years ago that we had, that they had arrested somebody for homosexual behavior in public, so that information came in from the police department.

Sometimes the information comes in from the physician, from the donor's physician. On occasion, the reports will also come in not necessarily at the subsequent donation, but shortly after the donation. Most of those are due to post-donation illnesses where the donors find out a couple days after they donate that they have come down with some kind of disease.

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Some of the sex partner risks are also provided shortly after donation where the donor now finds out that his girlfriend or boyfriend had some type of high risk behavior that he didn't know about until after they donated.

[Slide.]

I am going to give you some examples of the post-donation reports that we received for blood establishments and for plasma establishments. I separated those because some of them are a little bit different.

You can see the first one, the donor traveled to the United Kingdom has been the top of the list for this year. Since the implementation of that question, I think a lot of the blood banks began implementing it anywhere between like August, September to March. In March and April we saw a significant increase in the number of reports related to donors who had previously traveled to the United Kingdom.

Donor traveled to malarial endemic areas is another one that has been typically one of the highest type of information reported over the last several years,

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and this is mostly the donors don't remember that they traveled to a certain area or maybe sometimes they weren't asked completely to find out if they really were in malarial endemic areas.

Donor had a history of cancer. This is another one that for some reason donors don't remember that they had cancer. A lot of these are history of cancers that are permanent deferral, but the cancer may have occurred 10 or 15 years ago, and they are thinking that they are okay.

Some of these also are problematic because some of the doctors will tell the donors that yes, you are cured of this cancer, there shouldn't be any problem for you to donate, which may not be consistent with blood bank deferral policies.

Also, that dealt with the history of cancer, some of those, a small percentage of those are received by the donor shortly after the donation, because that is when the cancer is diagnosed, where the donor didn't have any information at the time of donation.

Donor reported post-donation illness is another one that has been very frequently reported. Most of

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these involve mono, chicken pox, viral or bacterial disease. This category does not include any diseases related to hepatitis or HIV.

Donor had a history of tattoo is another one that has been consistently a problematic area that the donors don't remember that they had the tattoo. Sometimes the way that I see the reports come in, and looking at the way that the question could have been asked, you know, if the question is asked have you had a tattoo in the last 12 months, if the question was asked since May of last year, have you had a tattoo, I have to wonder whether or not they would get a different response, because people may not remember that last May was 12 months ago, but that is just in looking at some of the reports that come in.

Like I said, about 70 to 75 percent of the reports, of the information that is reported, the donors know before they walk in the door, the donors have this information. It is only about 25 to 30 percent which would include the cancer diagnosed post donation and the post-donation illnesses that the donors don't know. So, there is an opportunity for us to get that information

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up-front. We just have to figure out how is the best way to get that information.

[Slide.]

Now, plasma centers, the most frequent type of information that is reported it tattoo and body piercing. For '99, it says 45 percent for these because in '99 and earlier years, we grouped those two risks in one major category. For FY 2000, we separated those out, so that 25 percent of the reports in 2000 have been related to tattoo and 14 percent related to body piercing.

A lot of the plasma centers get the information from either during the annual physical where they notice a new tattoo or they notice another body part pierced. That is how they get that information. A lot of times the donors won't provide that information.

Donor had a history of incarceration is another one that is very frequent in the plasma industry, and in this case, a lot of times the plasma centers get this information from reading the newspaper. The local papers will sometimes print out a listing of everybody who has been in jail for the last week or the last month, and then when they start recognizing donor names, they go

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back and say wait a minute, this guy donated last week, he has been in jail for the month before this.

Also, in plasma centers, there is also a lot of conversation between donors that is overheard by some of the plasma center employees where the donor would say, yes, when I am done here, I am going to go see my probation officer, you know, and it is those kind of things that the screeners and the phlebotomists seem to be attuned to, and will identify those donors.

Donor had high risk behavior that wasn't specified. We had a lot more of those type of reports submitted last year than we have this year. Those are just kind of unspecified high risk behavior where it just wasn't specified on the report, where the donor may have told the plasma center or they got some information that the donor was at some risk, in some high risk category, but it didn't specify on the report what that risk category was.

Donor had a history of IV drug use is more prevalent in the plasma center than it is in the blood centers at a smaller percentage.

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Donor traveled to the UK. We are starting to see some reports from the plasma centers, but not nearly as many as we have from the blood centers.

[Slide.]

Now, donor screening, I wanted to highlight donor screening because not only do we have to be concerned with the questions as they relate to the donors, and can the donors understand, but we also have to think about are these questions easy enough for the screeners to understand and to understand why they are asking these questions.

Donor screening captures any errors and accidents that occur from the time the donors walks in, the hemoglobin, hematocrit is checked, blood pressure checked, temperature, all of the questions are asked, and the donor is determined to be suitable or unsuitable including checking of the deferral list.

Again, licensed blood banks report the majority of these, unlicensed blood banks only a few, plasma centers, a little over 100. Donor screening represents about 5 percent of the errors and accident reports that we receive.

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[Slide.]

Now, for the blood establishments, the most frequent error or accident that occurs in donor screening is that the donor provides information of traveling to a malarial endemic area, but is not deferred. That has been consistent for the last several years. You can see it is at 29 percent for this year and the last year.

A lot of times this happens because the donors will say that I traveled to Mexico, but that follow-up question was not asked, where in Mexico did you travel, or they will say that they traveled to a certain area that is malarial endemic, but the screener won't pick up that it is an endemic area. They will think that oh, they must have meant this other area, or they just miss it completely.

Donor record incomplete, specifically, the donor history questions, or the donor history questions were either not asked, not documented. We have some cases where none of the history questions were asked, others where it is just certain ones were not asked.

Donor gave information regarding history of cancer. Again, this is something that probably pertains

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more to the deferral periods for some of these different types of cancer than anything else, because what may happen is that the donor will give information of a particular type of cancer at a certain period in time, and the screener may think, well, that is only a permanent deferral or because it happened so long ago, it is okay, when it should have been a permanent as opposed to a temporary deferral, and then they will accept the donor inappropriately.

The donor gave information regarding medication. This is one that I think happens because sometimes the screeners will focus on the disease. If the donor provides information of taking medication for a certain disease, the screeners may focus on the disease and say, oh, well, they had this disease, and that's okay, but they forgot that they have to focus on the medication, as well.

Donor gave information regarding history of disease. Again, that is the same permanent/temporary deferral. Sometimes the screeners aren't aware or it is not clear in the procedures of which ones are acceptable,

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at what time, you know, which ones are permanent deferral, which ones are temporary deferral.

[Slide.]

Plasma center donor screening errors and accidents. Most of those involved the donor history questions, where some of the questions or sometimes all the questions were not asked of the donor.

Medical review/physical not performed or inadequate is a small percentage, about 7 to 8 percent.

Donor temperature not acceptable or not documented is about 6 to 7 percent.

Donor gave information regarding vaccine or immune globulin seems to be a reason for problems in the plasma industry.

I bring up the issue about the screeners knowing why they are asking these questions and what the risks are because we have had some reports where you can tell that the donor screeners were just told they are supposed to ask the questions and write down the answers, and they may not be given all the information they need to make the right assessment.

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We had a report where the donor provided information that he had had an ear pierced, and the screener said I am sorry, you can't donate for 12 more months, and the donor said, well, I donated last time and told the screener that, and she said as long as I took the earring out, it was okay to donate.

You know, we have got to think about the questions related to not only the donor's understanding, but also the screener's understanding these questions, as well, and making sure that they have the right information to be able to get the information from the donors.

I will end it on that note. Thank you.

[Applause.]

DR. LEE: It was a very easy task to invite Sharon to give this talk because she has a vested interest in this. If you do a good job in streamlining the questionnaire, she will get far less reports to deal with.

So far our morning presenters have addressed basic fundamental issues and overall issues about the donor selection process, and now we turn our attention to

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more specific issues and we will start out with our first session which actually deals with the questionnaires directly themselves and its function as to how it reduces infectious disease risks and how it protects the safety of the blood supply, as well as provide adequate assurance that there is adequate blood.

Dr. Alan Williams will address the topic of how the donor questionnaire reduces infectious disease risks.

Dr. Williams.

ROLES OF THE DONOR QUESTIONNAIRE

How the Donor Questionnaire Reduces

Infectious Disease Risks

DR. WILLIAMS: Thank you, Jong.

[Slide.]

What I have been asked to do basically in this morning's and this afternoon's presentation is discuss how well the donor screening process does its job from a safety perspective.

The way I have chosen to organize this is in this morning's talk, I am going to discuss some of the successes and some of the deficiencies of the donor screening process where we do have data to provide an

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assessment, and then this afternoon, in the context of trying to look forward and how to define data needs for the future, point out what some of the data deficiencies are, what some of the difficulties are in collecting data and discuss that in a little more detail.

[Slide.]

So, to reiterate in just two slides here some of the things that Dr. Epstein opened with, what is the importance of accurate donor qualification. I think there are four major areas. By far the most important is to maximize blood safety both in terms of known agents where there is a laboratory screen, and I will say something about that more in a moment, and, of course, for unknown threats where there is no laboratory screening test available.

The second factor, it is important to have accurate donor qualification to minimize donor loss due to inappropriate deferral.

Thirdly, as just discussed, it is important to minimize negative operational impacts, such as from post-donation information, and one thing not mentioned yet, but I think is an important factor, is to minimize staff

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exposures to infectious donations. These are folks who are collecting a unit of blood not knowing what it might contain although there is universal precautions used in all instances, it is just best not to have that blood collected at all.

[Slide.]

As also mentioned, in the context of known agents, it is important to pre-screen donors before the unit is collected to eliminate those rare window period cases that might occur equally or even rarer is the consideration of testing errors that might occur. This is rare, but not nonexistent, as we saw from hepatitis C screening data discussed approximately a year ago at the National Meeting.

Of course, as already mentioned, release errors probably is the major contributing factor that is of concern in having infectious material in the blood bank at all.

[Slide.]

Just to establish some structure, what are the levels of donor qualification? I think this is important to keep in mind because we tend to sort of centralize our

thinking on the screening process as it occurs in the blood center, and I think as you listen a little bit more, you will begin to realize that, in fact, most of the screening occurs in other circumstances.

So, what is the first qualification? The exclusion of risk populations and this happened some time ago. That would include paid donors, as well as an example, exclusion of prisoners, and I think there is a lot of historical data to show that when these qualification measures were instituted, that the blood supply very quickly became safer, particularly from a hepatitis perspective.

So, there are historical data to address that.

A second factor is self-deferral before the blood drive based on educational information that is made available to a potential donor. There is extrapolated data to measure the effect of this factor. I will show you some of the data available. It is kind of in a sense comparing not apples and oranges, but apples of different types because the data is collected in different situations with different populations and different time frames, but you can begin to see some correlations.

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There is also the self-deferral process at the blood drive. When the new donor arrives at the blood center, they do receive educational information, and certainly an unknown proportion of those donors leave the blood site before going through the actual interview process, and we don't know much about that scenario at all except that it does occur and we try to make educational if available.

Then, finally, deferral by staff during the interview process. There is limited data. We know the numbers, but for the most part, there is not too much other information available about that.

[Slide.]

Now, I want to detail some of the successes of the donor screening process. The first one is reduction of infectious disease, marker prevalence, and where data are available, also measured in incidence and accepted blood donors.

Just to reiterate, prevalence is the number of markers present in the donor population at a given time. Far and away, virtually all of this is detected by the blood donor screening test.

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Incidence is new infection. It is related to the risk of window period and is part of the prevalence calculation just to give a little explanation for that.

How can we measure this? We can look at donor data versus the general population, and we can look at donor data over time.

[Slide.]

Just to look at a general population comparison for HIV, there was an estimate of a little under a half percent HIV seropositivity in the donor age general population. I believe this reference was from the CDC Household Survey. Comparing that in the same time frame, around 1995, the HIV prevalence in first-time donors was 0.03 percent. We want to use first-time donors because there hasn't been a pre-screening effort working, and it gives us a better comparison of what the educational factor might have contributed.

Compare those two numbers, you are looking at approximately a 15.6-fold reduction in risk in un-laboratory screened potential donors coming through the door.

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Looking at changes over time, these are data from the CDC-sponsored seroprevalence of HIV in blood donors. These happen to be American Red Cross data and broken out by gender, but you can see a definite slope, a downward slope in the time frame from the 1988 starting point through 1997.

I don't have first-time and repeat donor data separated here, but you can be pretty well assured that the downward slope is caused by the reduction in prevalence in the first-time donor population. The repeat donor population, once the screening had culled out seropositives, the repeat donor population is fairly stable.

So, you can see a reduction over time, and I would attribute this due to broader knowledge about the criteria which created an acceptable blood donor and knowledge in the general population of who can and who cannot donate.

[Slide.]

Shown here is a graph from one of Mike Busch's chapters showing the situation in San Francisco. This is

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a performance of the screening questionnaire in what we would call a crisis situation.

In San Francisco, obviously, the epicenter of the early AIDS epidemic, I can barely read those dates, but around 1981, the first AIDS cases were reported. These are estimates of the risk of post-transfusion HIV transmission based on retrospective looks at donor prevalence.

The first AIDS cases were reported in 1981. The first post-transfusion AIDS case was reported in 1982, and in the same year, high risk donor deferral was initiated. What is barely visible in the slide is a little upward slope that you can see continuing from that initial rise.

That would be the continuing increase in post-transfusion transmissions had high risk donor exclusion not been implemented. You can see at its peak there was about 1.2 to 1.3 percent risk per unit of blood.

Then, you can see the curve coming back down. The second to the last factor, HIV is discovered, and there is a progressive impact of high risk donor deferral. Then, once HIV was implemented in actually the

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spring of 1985, you can see that risk dropped off, but for the most part, the bulk of the danger had been removed before donors were actually collected and the screening test was in place. So, although this was certainly a very tragic situation, it is a good example of how the screening measures do work in a crisis situation when there is no test available.

[Slide.]

The other way to assess changes in potential blood safety or compromised blood safety is to look at the reduction in measurable risk in the blood supply, and again versus the general population and over time.

[Slide.]

So, looking at education and interview-based deferrals versus the general population, an estimate from the NORC facility in Chicago estimated that males who had sex with other males at some point in the past five years constituted 4.1 percent prevalence in the general population.

As some of you are aware through the REDS study, we have been doing survey research in accepted donors, and we actually established a factor first in 1993 data

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showing donors who were accepted as blood donors, who had a risk of males who had sex with other males since 1977, we measured about 0.6 percent in the donor population. So, although this is certainly not ideal to have that degree of risk remaining in the donor population, we still see a 7.2-fold reduction.

[Slide.]

Similarly, for IV drug use since 1978, the Dallas Household Survey in '94 estimated that at 3.9 percent. The survey from the REDS study estimated 0.5 percent, so a similar reduction in risk due to the questioning process.

[Slide.]

So, just as a summary statement for the successes, donor qualification measures have contributed to what really is unprecedented safety of the blood supply, and this has been in combination with laboratory testing and other procedures. I think we can't lose sight of the fact that a lot of the things that we have worked hard to do over the past 15 years have made a real difference, and the blood supply is really very safe.

[Slide.]

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What are the current transfusion risks per unit? These figures are actually brand new. These are some that Dr. Roger Dowd put together for his annual seminar presentation on blood safety risk, and they are based on 1999 incidence data from the Red Cross system, and I think probably represent the latest estimates of risk that are currently available.

For HCV, in the absence of NAT, which of course we are doing, the risk estimate would be 1 in 237,000 per unit. That is reduced half by NAT testing, which is in place in all blood centers now. HBV risk is 1 in 137,000. There is no NAT currently in place. HTLV similarly, 1 in 641,000 with no NAT.

HIV, I think is really the impressive figure where the risk in the absence of NAT would be considerably less than 1 in a million, and in the presence of NAT, now is approaching 1 in 2 million.

[Slide.]

To look at some of the deficiencies, we have alluded to some in the context of the other discussions, but one of the major points, there is interviews with

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seropositive donors, regularly revealed behavior risks that should have prevented donation.

These studies have been available for a long time even back to the early hepatitis days. It is easy to identify seropositive individuals. When they are interviewed, often they have factors that should have prevented their donation.

[Slide.]

Only recently have we tried to quantitative these on a larger scale. Again going back to the CDC-sponsored study of HIV seropositive donors, I am thankful to Ken Clark for this slide, and he is in the audience.

These are risk data looked at in two different time frames for blood donors identified with HIV risks. In males, comparing in 1988 time frame to 1997, the red reflects male sexual contact with other males.

You can see while it is reduced from approximately I would say 55 percent down to closer to 30 percent in the 1997 data, that risk still is in evidence in blood donors found to be HIV seropositive.

You can see a concomitant increase in the no-identified risk group. Similarly, in males, while a

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larger proportion in females have no identified risk in the question interview following detection of seropositivity, that factor has increased and the other major factor in females, known heterosexual contact, still a large factor, but somewhat smaller in the later data.

This is just to reflect the fact that in this highly selected population, risk still is evident.

[Slide.]

Risk is measurable in accepted donors, and here are some data published from the first major REDS study. These are 1993 data published in 1997. We actually had the first quantitation of risk in the donor population with factors generally ranging from 0.1 to 0.5 or 0.6 for the major risk factors that we are looking at.

Very briefly, the methodology used here, this is an anonymous mail survey which was sent to active blood donors within six weeks of their donation event, so that we are actually getting recent donors who presumably have recent recall of their screening history and we were able to capture these risks which we call deferrable risks that should have prevented their donation.

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In summary, about 1.9 percent of donors reported one or more deferrable risks, and to translate that into the overall donor population, it is about 242,000 individuals per year.

We have repeated this survey both on a pilot and a larger scale, the 1998 survey found very similar data when the risks were defined the same, but in fact, interestingly, when you add some of the less specific questions, like tattoo use and birth in Africa, and so forth, the risk factor overall climbs up to about 3 percent.

[Slide.]

We are able to correlate some of these risks with other factors. I have shown just a few here. The confidential unit exclusion, which was made voluntary at blood centers, still used by some, CUE use overall in non-risk males is about 0.3 percent. In males with defined MSM risk, it is 2.9 percent for an adjusted odds ratio of 9.7, and that is adjusted for these other demographic and behavioral factors shown below.

Privacy was mentioned earlier. About 5.6 percent of non-risk males say on the questionnaire that

they wished they had had some higher level of privacy. That is even higher for MSM males, 16.2 percent with an odds ratio of 3.2.

HIV test seeking, an important factor, about 6 percent overall for non-risk males, 16.2 percent in MSM males, for a significant odds ratio of 2.9.

So, we are starting to get a little better understanding of some of the factors that relate to this risk.

[Slide.]

These two observations aren't strictly correlated or they can't be strictly correlated, but I think it is an interesting observation here, that in the data from the 1997 CDC HIV Interview Study, of all the HIV-positive MSM donors interviewed, 90 percent reported MSM activity in the past year. So, these are high-risk individuals who are continuing MSM activity right up to their donation point.

In the 1998 REDS survey, we identified a little under 0.6 percent of males who had MSM risk and 14.7 of these on the survey reported MSM activity in the past year. So, this would equate to about 5,400 high-risk

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individuals in the blood supply, obviously, not all of whom have acquired HIV, but these are the population where the HIV infection is originating. I think that is an important factor.

[Slide.]

Behaviorally, there is a lot to talk about, I am not going to discuss it all, but interestingly, I think if you look at the data, the on-site questioning is the most costly in terms of donor loss and burden, et cetera, and is probably the least effective donor qualification element.

Looking at some of the numbers I have put up recently, the 4.1 percent estimate of MSM in the general population, 0.6 percent in donating males, actual on-site deferrals for MSM activity is reported by Dr. Bianco several years ago in a workshop, and also agreeing with some of the Red Cross data, is on the order of 0.01 to 0.03 percent of on-site deferrals, so most of this deferral is taking place before the interview process actually happens.

[Slide.]

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Relating that to more recent deferral, the UK estimates, most of you are familiar with the survey work that was done before implementation to consider the loss of donors. We found on our pilot survey that 2.4 percent of donors responding to a survey indicated that they had travel that would put them into a deferral category.

As most of you are aware, the on-site deferral experience is much lower than that, again, 0.1 to 0.3 percent, so it is a little hard to tell exactly where these deferrals are happening, but again, the on-site experience appears to really be the lowest factor.

[Slide.]

Just a behavioral perspective. Donors seek to gain or preserve something of value by proceeding with donation. This can include test results from free confidential reliable sources, such as blood centers, a healthy feeling and altruism derived from donation itself, saving face in a pure environment, and other possibilities.

I mainly included this just to reinforce the fact that this really is behavioral science that we are

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talking about, trying to influence people's behavior and get them to self-identify and defer.

[Slide.]

In conclusion, donor risk education and screening is critical to helping protect the blood supply from both known and unknown threats. Donor risk education and screening currently reduces the risk burden in the donor population by 7 to 15 percent, and it could be higher or lower depending on which data that you use for a comparison.

On-site interview is likely to be the least effective component of the education and screening process. You can argue that it is the last chance component, but in terms of numbers, it really does not add terribly to the process.

Finally, the behavioral dynamics and the education and screening process are complex, and as I will emphasize in this afternoon's talk, there is a real need to input some behavioral science into the design of the screening questionnaire.

I will stop here. Thank you very much.

[Applause.]

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DR. LEE: Thank you, Dr. Williams.

In view of our comments, perhaps we should be focusing much more attention on everything that happens prior to the questionnaire itself, but nonetheless, we proceed.

To continue the story of the role of the donor questionnaire, we will now have the pleasure of hearing from Dr. Celso Bianco. He is well known to everyone. I tried my best to keep him out of this workshop, but here he is again, presenting data once again.

Dr. Bianco will speak on the issue of impact of current screening practices.

Impact of Current Screening Practices

DR. BIANCO: Thank you, Jong.

[Slide.]

It is wonderful that we are discussing these issues today. I really want to thank FDA and AABB for leading that effort. I think this is the major contribution that we can make to the blood supply and to transfusion in the country.

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I am going to review data accumulated over the years. Obviously, I can't avoid but repeat some of the things that have been said here.

[Slide.]

Medical history in the past was it. We didn't have much to do, and there were no screening assays except for blood typing. The history of infectious disease is obviously focused on hepatitis, and I just want to remind you of some studies that were done by the Academy of Medicine in New York showed that 25 percent of patients receiving multiple transfusions at that time developed hepatitis, clinical evidence, jaundice.

[Slide.]

Because of that heritage, I think that we created some assumptions that we are still dealing with today and that probably are an obstacle to us being aggressive in terms of changing what we do.

We saw a lot of success. We heard a lot about the success, and I will show a little bit more from Dr. Williams, but we have unrealistic expectations from medical history. Those expectations are not really based on data. We think that all questions are understood by

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all donors, that all donors are truthful in their answers, the more questions we ask, the better, and certainly that has created a little bit issues, the issues that we are trying to deal with.

We continue to add complexity to medical history. There are too many things and too many questions. Sometimes I think, I sit when I donate and I try to pay attention to what the historian is asking me, and even for me, that know all the issues, discuss all the issues, it is boring. It is too many strange things that people never heard about and they are bombarded with all these series of things, I think that it is very hard to remain rational during the process.

Many questions create political anxiety or behavior anxiety, and people sometimes respond in a different way, and I have this bias, and it is my personal bias, I don't have data, but because of all the movements that have been occurring in colleges and other places regarding the deferral of males who had sex with males since '77, and classifying it as an unfair question, that many of these numbers that we saw from Dr. Williams come as a reaction to that, not because the

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donors want not to be truthful, but because they are angry about these types of questions.

We know from the AIR that we are going to hear that these questions, the complexity interferes with the accuracy of answers and that we have no clear means of validating the impact of additional questions and the changes that we make to the questions on the overall accuracy, on the final product of our medical history.

[Slide.]

I want to add to what Dr. Williams said. Medical history works because donors respond, and it is incredible, the honesty of many of the donors. A large number of donors reveal to us that they have taken drugs or that they had sex with another male.

[Slide.]

When we added direct questions in 1992, we can see that these had a tremendous impact. The number of donors that responded yes to the fact that they had an increased HIV risk tripled, while the number of donors responding to other standard questions or deferred to other reasons remained more or less constant.

[Slide.]

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Cocaine was another one that because of some information in a study that had been performed at NIH, there was a correlation between the use of intranasal cocaine and hepatitis C. Simply adding that question, have you used cocaine in the last years, yes, we had a number of donors saying yes.

[Slide.]

So, donors reveal risk behavior, however, these donors are deferred up-front and specimens are not collected for testing, and I think that that would be the most important study that we could do to understand the impact of medical history.

I would like at this point to actually separate two things. One is the selection of the donor base. Dr. Williams actually clearly showed that. By the way we select donors, by the way we recruit, by going to organized segments of the society, schools, churches, corporations, certain communities, we are selecting healthier organized segments of the population are people that believe in altruism, are people that believe in doing some duty to the community.

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We don't know how to measure that, but I think that this contributes a lot to these two logs that Dr. Epstein referred to and Dr. Williams between what we see in the general population and what we see in the population of first-time donors.

We don't know, for instance, if really deferring the individuals because of cocaine snorting in the last year, if we actually reduce the number of individuals that were HIV-positive, for instance, that came to the system. So, we don't know, and Dr. Epstein remarked very clearly the sensitivity, the specificity, the positive predictive value or the negative predictive value, and I wish we could measure it.

[Slide.]

CUE is another that Dr. Williams showed very well that has a correlation with behavior, but CUE has been losing its effectiveness in a certain way.

[Slide.]

I thought that Ken Clark's data and the data that we see as we see the number of individuals that use CUE gradually decreasing. In '98 and '99, we did not have any HIV-positives selecting CUE. This is reflected

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in the change in the demographics of the population that we saw very clearly in that slide from males who had sex with males usually are more sophisticated, more cultured population, more organized, that understood the risks of HIV in the beginning, to a population now that has more minorities, lower social class, more women that do not really understand the sexual behavior of their partners, so that CUE, the confidential unit exclusion just saying don't use my blood has no meaning. They do not understand or they do not know the risk they were exposed to.

[Slide.]

So, CUE was effective. Today, only a small proportion use it. Very few, if any, of the donors that today use CUE is positive, and that is associated with the change in demographics.

[Slide.]

However, we defer a large number of donors because of our questions. That actually is a big cause of frustration for the donor that finally amass the courage, either pushed by their peers in the church, of by themselves, that they were going to do it, and come to

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a very frustrating experience in which they were denied that privilege of contributing to the blood supply of the community.

I did an analysis of deferrals at the New York Blood Center in 1998. At that time, 13 percent of all donors that showed up to donate were deferred. 5.3 percent were deferred because they did not pass the hemoglobin test, the 12.5 grams of hemoglobin, and interestingly, we have not talked about sex differences here, but over 90 percent of those are women.

One percent or 1.2 percent because of physical measurements that prevented them from donating, temperature or blood pressure, theoretically objective, even if I see a lot of variability within the system, but then with general questions, we defer another 6, almost 7 percent of our donors.

[Slide.]

When we rank the deferrals, it is very interesting and I highlighted some that are quite important. For instance, in the piercing, history of transfusion of blood, what I did, I extrapolated to the number of donations in the whole country that would be

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based on a survey of 4 million donations that we did among America's Blood Center members.

We defer about 85,000 people on the basis of piercing or transfusion, 90,000 on the basis of prescription medications, things that I feel in a certain way that need some refinement.

We defer about 50,000 people a year because they had a history of traveling to a malarial zone, and exposure to hepatitis or history of hepatitis, more importantly, about 13,000 people a year.

[Slide.]

The other deferrals are less important in terms of numbers, but they are more important in terms of--this does not include obviously, the new deferral in CJD--but certain things that are very important among the things that we do. There is about 6,500 people are deferred because they had needle tracks in their arm in the country, and that is a fair important, and a deferral that should take place.

[Slide.]

When we look over the years, deferrals have been increasing, and I think that there are a multitude of

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factors that lead to that, from the increase in the number of questions, the complexity of the questions, and things that we add, to a bigger concern about compliance. In a certain way, there is a confusion between what is medical, in fact, there is a big emphasis in terms of quality, in terms of compliance, in terms of following what is written and doing the right thing.

[Slide.]

If we try to see among first-time donors, we are actually deferring almost 22 percent, 23 percent of the first-time donors in 1999, that showed up at the New York Blood Center.

[Slide.]

In terms of repeat donors, it is still a substantial number. Obviously, many of those will be deferred either because of hemoglobin or because of some cold or not feeling well, but it concerns me that even in a population that we know, a population of repeat donors that are continuously there, that we are deferring such a large number of individuals.

We know that the incidence of disease in this population is very small, as reflected by the tables in

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risk that Dr. Williams presented to us. So, there is something wrong there.

[Slide.]

When we look at deferrals, there are certain deferrals that are more or less constant and probably reflect what happens in society, like the tattoos, they go around 0.75 percent, but when there has been an emphasis on the part of FDA, for instance, in malarial deferrals, we see a substantial increase in the frequency of malarial deferrals in the last several years.

[Slide.]

Deferrals because of tattoos and body piercing, while they are important, and while there is discussion about an epidemic of body piercing in the country, it doesn't seem to reflect substantially in the numbers as they grow. The numbers have grown, but they have not been overwhelmingly highest.

[Slide.]

Now, the problem with deferrals is that donors hate it, they feel humiliated, they feel rejected, and they don't want to come back.

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I analyzed a period. I took a period of about a year and a half between '96 and '97, and I asked how many donors that had been deferred have donated again even once by June '99, that is, two years later after the end of the initial period.

The dropout rate is incredible because of a donation reaction, but because of all these questions. Those donors really, even if they have the peer pressure, even if they are part of regular groups, the experience does not encourage them to come back. I think that there has to be more of an understanding, even if there are publications about deferred donors and their behavior, I think that we have to understand better how they feel, so that we can convince them to come back.

[Slide.]

There are still many issues that we have in medical history and that the workshop is trying to address, and more importantly, in the medium- and long-term, the AABB task force. We recognize that the questions are not always focused on deferring who should be deferred, and accepting who should be accepted.

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They have been written for 100 percent sensitivity, and that is why they are cumbersome, as if screening tests did not exist, as if the layer of safety was the only layer of safety that we had. They still have unknown sensitivity and specificity, and they lead to many temporary deferrals, many temporarily deferred donors do not donate again.

[Slide.]

I would hope that we can achieve maybe by the end of the day or the end of a few months, or by 2001, when Dr. Fridey delivers her report, is that medical history will be placed in a context of new technologies, NAT, for instance, that the weight in medical history, in hepatitis C and in HIV prevention, and even probably in hepatitis B, hepatitis B because by the time that this report is delivered, I suspect that we will be doing that for hepatitis B, maybe we should reduce the emphasis on those questions, not eliminate. That is not what I am proposing, but that should not be the major goal in medical history. There are other things that we want to prevent in medical history.

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We are going to hear also about computer-based interviews because they provide a substantial opportunity for improvement.

[Slide.]

There are still many approaches that we can eliminate questions better covered by technology. BPAC has addressed history of hepatitis. We have discussed in an FDA workshop risk behavior in the distant past. Thinking about 1977, has nothing to do with the real dangerous risk behavior in the last couple of weeks, focus on diseases and risks for which we do not have screening tests, bacterial infections, certain travel history.

[Slide.]

We should continue supporting the REDS studies. We need to monitor the prevalence of markers among eligible donors, and we need to determine the sensitivity and specificity of medical history questions by studying deferred donors. We need to determine the ID marker prevalence among the deferred donors.

We have to know what is the benefit that we are getting from all these efforts, all these hours that we

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apply, and the number of donors that we defer because of that process.

[Slide.]

This was my estimate, and this is my last slide, from the ABC Survey that we carried out about a year and a half ago. We deferred 2 million people from donating blood every year, and I am convinced that we could recover a substantial number of these donors if we were more rational in our medical history and more focused on real risks.

Thank you.

[Applause.]

DR. LEE: Thank you, Dr. Bianco.

That brings us to our first gap, so to speak, in today's series of presentations. At this point, I would like to ask all presenters to come to the front and provide an opportunity for the audience to ask some questions.

While the panel is assembling--this is sort of a mini-panel--I would ask all questioners to identify themselves for the purposes of the transcript, name and affiliation, please.

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Dr. Epstein, you may or may not join. I think you delivered far more than simply opening remarks, so I think it is appropriate that you join us.

Are there any questions from the audience? Dr. Simon.

Questions/Answers

DR. SIMON: I guess this will be primarily for Dr. Bianco, but any of the other individuals will certainly be welcome.

DR. LEE: Your name and affiliation, please, just for the transcript.

DR. SIMON: Dr. Toby Simon, Serologicals Corporation.

One of the questions I would like to pose is to what extent, particularly from Dr. Bianco's data, are the extent of deferrals from the required questions, either the AABB standard questionnaire or the FDA requirements, or to what extent do they exceed those and represent medical policies that are generated by the particular organization.

In other words, even if we were to streamline the questionnaire and the FDA were to change some of

these requirements, would many of these deferrals still continue?

DR. BIANCO: That is a very good question, Toby, I don't know the answer. I saw for the first time in Joy's presentation today that clear subdivision of what is required and what is not. I think that all of us in blood centers at least have combined all of them and tried to get the best we can, so that we make sure they fulfill all the requirements, but we have not measured the impact of the removal of each one of the questions on the overall deferral. It can be done, at least I have I believe enough raw data that I could try to do it for some of the past years.

DR. FRIDEY: If I could also add to that, Toby, the surveys that went out to the AABB blood collection facilities and to plasma centers back in August, most of them have come back. There has been about a 90 percent response rate.

We asked the responding centers to include copies of their donor questionnaires, which I will add pretty much have the required questions, but in very

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different order than the uniform donor history questionnaire.

Some centers do have a few additional medical history items, but really not too many of those, so I think even if you were to exclude the items that are added by individual centers, that you would not see a huge change.

MS. O'CALLAGHAN: Also, some of the reports that I do get related to post-donation do reflect certain establishments' own procedures in deferral. Where the information is provided, a lot of it, I think the majority of them refer to history of cancer, where there is permanent deferral in some establishments, but a temporary deferral in others, but because there is that temporary deferral in the one establishment, when the information comes in from the donor that the donor had the history that was in that deferral period, that would be reported under post-donation information.

But most of the post-donation reports that we do get are related to a required FDA question.

DR. LEE: A question in the back.

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MR. HEALY: My name is Chris Healy. I am with the Plasma Protein Therapeutics Association. My question is for Sharon O'Callaghan.

You present a lot of interesting data on error and accidents, and particularly with respect to tattoos and piercing and incarceration. I am wondering whether there have been follow-up reports or in the process of getting those E and A reports, whether there is any information about seroconversion from those donors.

It struck me as you were speaking that if these tattoos and things are discovered during the annual physical, and if they are not testing positive, raises questions about the utility of that kind of questioning.

MS. O'CALLAGHAN: That is one of the same questions that I ask when I get some of these reports, because especially with the plasma center reports, many times there are multiple donations affected by that, because these donors are donating, you know, every two or three days, over a period of a year, and the tattoo or piercing is only discovered at the annual physical, there is a lot of donations that have been affected by that high risk behavior, and there is no indication that there

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has been any seroconversion of the donor or that any of those units ever tested positive at any point, and most of them, a lot of them had already been sent and even fractionated.

DR. JACOBS: Mary Beth Jacobs, FDA. It is a question for Dr. Williams or others.

When you look at the motivation of test-seeking behavior, have you ever examined blood centers--and I think Dr. Gilcher's center does this--where they have available tests which people can pay for to see whether that reduces test-seeking behavior?

DR. WILLIAMS: That is a good question, Mary Beth. I think, to answer it, no, we haven't looked at that specifically, but we do have the capability to do it since Oklahoma is one of the sites, and Ron will have something to comment on that.

The other factor to look at is whether or not the center asks the question of the incoming donors whether or not they are appearing because they are interested in an HIV test. That is the other variable that we can look at, but we don't have those data.

I think Ron had a comment on that same question.

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DR. LEE: Is it a question or a comment?

DR. GILCHER: Comment.

DR. LEE: Please proceed.

DR. GILCHER: Addressing the last question, many, many years ago, it must be at least 12 or 15 years ago, we began offering what we called non-donor testing. It is exactly the same package as we do for donor, and an individual coming to a blood donation site can, in fact, request that these tests be done.

Now, interestingly, we charge the non-donor for those tests. What we found is that a lot of people wanted testing done in a very confidential or private manner, that is, they did not want to go to their doctor's office, they were willing to pay for that testing. I think that is interesting.

When we look at the results of the non-donor testing, what we find is that there is a higher incidence of positive viral markers. Our interpretation of this is that this actually has improved the safety within our blood supply by allowing these individuals to have testing done in a very confidential manner, but they were willing to pay for it. They were test seekers, but they

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were not necessarily--and I am not saying this is true for all--but they were not necessarily test seekers for free testing. They wanted the testing done in a confidential manner where they didn't have to go to a physician's office where somebody in the office knew who they were.

DR. LEE: Dr. Epstein.

DR. EPSTEIN: This is in a way a related question. It has been stated several times today that it would be very useful to gather marker data on the deferred donors. Many of us have recognized this for years and years.

The question is what is the obstacle to getting that data. Clearly, one of the problems is cost, somebody has to pay for that test when there is no unit collected. On the other hand, I am hearing that there is at least one modality in which it works.

Alan, I wondered if you could comment what the obstacles have been and what is the feasibility for that kind of study.

DR. WILLIAMS: Well, I can start to answer that, and Sharyn Orton, who is in the audience, actually did

some work putting together a proposal for a study similar to that. I think probably the initial obstacle is just the numbers of samples that you need to collect to get an outcome measure. Even looking at infectious disease NAT testing, it requires an awful lot of samples.

If you take the approach that you are going to get a sample on everyone coming in, there are the logistics of getting the actual sample before they donate the unit of blood. It would probably involve an extra informed consent process. Then, you would have the samples, when they are deferred, before the unit of blood is collected.

Doing the alternate design, which is to approach those individuals who are deferred and asking them to enroll in a study, give a sample, and answer a few questions, that is perhaps the most efficient say to do it, but there probably is a serious bias concern with those who would be willing to enroll in such a study and have testing done.

So, those are the two concerns, and I think the bottom line is, is that big, expensive effort going to be worth it, will we produce convincing enough data to cause

a change in policy, and I think that is really an unanswered question at this point.

DR. LEE: A question in the third row.

DR. CHIAVETTA: Jo Anne Chiavetta, epidemiologist for the Canadian Blood Services in Canada.

Some of this data has been presented at AABB or published in a recent July issue of Transfusion Medicine Reviews, but just to reiterate some information. When we were talking earlier, the speakers were talking about discouraging donors before they either get to the clinic or before they actually go through the donation process.

It seemed some findings that we have really say that that is very important. There are two studies that I have done very similar to the REDS studies across Canada. These are random samples of all Canadian blood donors.

The first survey was done in 1996, and it was a mailed survey, very similar to Alan's work, and we had about 6,000 donors. About 7 percent of those donors reported deferrable risks, that is, an exposure within the last 12 months of donation, the previous 12 months, or male homosexuality or IV drug use in their lifetime.

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Between that and the second survey, which was done on about 3,000 donors in 1998-1999, we instituted regulatory compliance program, which really focused the questions on the donors very much more, you know, more focused questions, more regulation regarding how the questions were asked. Again, we found 7 percent of the donors reported at least one deferrable risk, very similar risks than before.

In both data sets, it was interesting to note that when we looked at who these people were, who were the people coming in, there was a huge number of people that truly did not believe that their behavior was at risk, because they were asked questions, third party questions, who should donate blood and who should not, people who reported deferrable risks were much more likely to actually believe that people who did these various things were fine, they were okay to donate. So, they actually truly didn't seem to understand the issues, the education hadn't worked.

The second thing that was disturbing in both time periods is a huge proportion of these people with risks also were acknowledge test seekers.

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DR. LEE: Thank you. Does that perhaps mean that we should be concentrating on donor education once again, a theme that Dr. Alan Williams set out very clearly, rather than the questionnaire, but that is still within the scope of our workshop in terms of the donor selection process.

We have a question on the left side.

MR. WILCZEK: Joe Wilczek, FDA. This question is directed to Dr. Fridey.

Once your task force has completed making revisions to the donor history questionnaires, how will you go about or proceed to validate those changed questions?

DR. FRIDEY: That will depend on the kinds of changes that we think would be appropriate, that will determine the designs. We have a meeting tomorrow with the task force, and we will begin to look at those kinds of issues. We are still right now in the data collection process.

We haven't analyzed the information that has come back from the survey that went out to blood centers recently to identify problematic questions. We have to

look at that, and the data that we get back will help determine it, and the changes that we feel are appropriate will determine how we are going to approach the study design.

I think we have to be realistic about what we will be able to do given the fact that at this point in time, there are no research dollars on the horizon. We are hoping that if we have to get into involved projects, that government agencies and other organizations or the industry itself may be able to help out. So, we do have some resource issues with which to deal.

I am sorry I can't be any more specific than that, but we have to first collect our data, see what changes we want to make, and then go from there. Thanks.

DR. LEE: Dr. Epstein.

DR. EPSTEIN: One for Celso. You commented on the need to reexamine questions in the light of testing and create better complementarity.

Do you have any specific examples in mind where you think we might do that?

DR. BIANCO: Yes, and there are examples. I don't know if they are correct, but one of them that we

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addressed recently was the history of hepatitis. I think that the quality of testing in hepatitis and what we do in terms of hepatitis really, as discussed at the BPAC, they don't contribute much to the tests.

So, when we have a very good technology, when we see a risk with the current approaches to 1.9 median for HIV, I would reduce the emphasis on questions of HIV and take questions on hepatitis, and focus those questions more and better ask the questions about malaria, so we become more specific, better ask the questions even about CJD helping people. I am sure that a lot of the people they are deferring about CJD, don't understand the six months and the year, and all that.

I am saying it just superficially, but that is what I would like to study, I would like us to try to do.

DR. EPSTEIN: I guess what is bothering me is that there is a distinction between histories that may be obsolete and that they don't add anything currently, and histories that are not obsolete in the sense that they are eliminating communicable disease risk, but that their sensitivity for doing so is far less than current testing.

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So, for example, it would be hard to argue that the behavioral exclusions don't contribute to safety because we believe they are eliminating both window period risks and also risks for inappropriate unit release.

So, the efficiency of that approach is low, but it is certainly non-zero. It is easy to argue the case where there may be negligible added benefit, such as history of hepatitis, but it is a lot harder to argue the case where they are both contributing, just not in equal measure.

So, can you talk about one of the harder cases?

DR. BIANCO: I don't know exactly how to answer, and I think you have a good argument, but I think that you made a very nice point early when you started discussing risks and benefits.

I wish that we could take that table that Alan presented and put it in the circular of information, and say every time you transfuse a unit of blood, you are going to expose your patient to this risk, because the risk of every unit is about the same. What varies is the behavior of the physician that is transfusing the unit

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and the judgment of that physician in terms of what is the risk that he or she is willing to expose that patient.

I think that the questions have more or less, if we are approaching it from going to zero risk, yes, every question ultimately, by itself, would add. My concern is that that overall, that the sum of the questions is less than each one of the questions because they are confusing, they are complex, and they divert the attention of the donor from that.

I think that the risk behavior is one of them. I wish we could ask the questions only what have you done in the last month in terms of risk, have you had sex with a prostitute, sex with another male, but just the last month, forget about the last 25 years.

That is the kind of focus that I dream we will be able to get to.

DR. LEE: Mr. Gill Conley.

MR. CONLEY: Gill Conley, FDA.

Dr. Bianco, you present data that shows the reduced likelihood of people returning to donate within a year after being deferred. What is the baseline on that

data on all donors? Your range ran from around 22 percent out of 70, and I am just wondering among all donors, what is the likelihood they won't be back in a year.

DR. BIANCO: It is more than a year because the average for us--and I am using New York data--but I think the national data and audit data are not that different. About 85 percent of our donors are repeat donors, but they are repeat donors, that is, they donate an average of 1.5 times a year only, they don't donate more frequently than that.

It is very different for first-time donors and repeat donors obviously. First-time donors, they donate once and 60 percent of them disappear from the face of the earth, they never come back. Obviously, those are individuals that donated, are not this 23 percent that simply were deferred because they came with a history.

So, the predominant value here in the 70 percent and 30 percent are in the repeat donors because they weigh more, and those are the individuals that will donate 1.5 times a year. That is the background rate, that is, they are repeating 1.5 times a year.

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MR. CONLEY: So, the table itself was from already repeating donors.

DR. BIANCO: I did not separate them. Yes, they are repeating donors, because if they didn't come back--they were all repeat donors, but I have to recheck actually the source of the data. You asked a very good question. It has been some time since I analyzed the data, I want to make sure. It is a very good point, but I believe I only took repeat donors into the table.

DR. LEE: I think this will have to be the last question.

AUDIENCE: This is primarily for Dr. Williams and Dr. Bianco, and given the comments you have made about education and pre-screening and things like that, and the lack of use of credentialed staff, I am wondering what your thoughts would be on using a fact sheet that is well written, standardized, to give the donors, particularly on the HIV questions, and then saying have you participated in any of these risk behaviors as opposed to going through each and every one of those questions and them being tongue twisters, the staff maybe

not understanding how to explain, the donors not understanding what is being asked.

DR. BIANCO: I think that this is very reasonable except that I remember an old study saying that only 27 percent of the donors really read the fact sheet that we give to them, that is, we give one that says what you need to know about your blood donation, telling them about the risks, telling them about what will happen to the test results, and of those 27 percent that read it, a good number of them don't understand it.

So, maybe your concept is correct, but we have to use other things, maybe a videotape, maybe a more interactive computer, educational program. There are many new technologies coming out, and it is not my expertise, but people do it for so many other things that are less important than that.

DR. LEE: A follow-up comment.

DR. WILLIAMS: One thing I will add briefly, I think a lot of these materials are in place, on site, when the donor first comes through the door and the waiting period before they actually start talking to staff members, but I think there probably is opportunity

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both to implement and then evaluate the value of using this information prior to a blood drive at a given site, be it a work site or an educational facility, and try to reinforce this before the blood drive educational loop, because that clearly is one of the areas that hasn't been well evaluated, and I think the data sort of point to the education factor as being a major component in pre-screening donors. So, I think there is opportunity for that.

DR. LEE: Dr. Gilcher.

DR. GILCHER: Alan, I think you are aware, as others are here, that we designed a brochure, if you want to call it that, a number of years ago at the request of a focus group at OBI. It is called, "Why all the Questions?"

Specifically, this was done to explain the questions. It is not the answer to the questions, but it is an explanation in more detail of the questions.

Our problem really was disseminating this among donors, individuals, before they donated. It has been very successful, but not nearly as successful as we would have liked. I will remark about this during my talk. We

are now going to put that onto our web site on the Internet, so we will have that explanation of the questions again, not the answer, but the explanation of why we are asking the questions, aimed at trying again to improve the safety of the blood supply.

DR. LEE: Thank you. In the interest of staying on schedule, I think we will end our question session here and we shall have a 15-minute break, to promptly reconvene here at 11 o'clock.

[Recess.]

DR. LEE: To continue the discussion of the roles of the donor questionnaire, we will now hear from Dr. Toby Simon on the source plasma side of things, and his talk is entitled, "Source Plasma Deferral Issues."

Dr. Simon is the Vice President of Medical and Scientific Affairs of Serologicals Corporation. He is also an adjunct professor of medicine at Emory University School of Medicine, and he currently serves as chairman, Medical Director's Committee of ABRA and is industry representative on the FDA Blood Products Advisory Committee.

Dr. Simon.

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Source Plasma Deferral Issues

DR. SIMON: I am very pleased to be here and appreciate that the task force and the FDA have invited the plasma industry to participate. We do have an urgent need to increase the number of plasma donations to serve the patients who depend on these donations for the quality of their life or for their survival. So, for us, anything that can be done to streamline and within the parameters of continuing our safety record, would be extremely important and extremely helpful.

Given that so much of the discussion has focused on the blood donor, we want to make sure that it is understood that plasma donors are essential and that some of the things that are being done to streamline the questionnaire and to deal with this issue can be very helpful in the plasma environment, as well.

Just to review quickly, the plasma program in the United States is under the Quality Plasma Program of ABRA, which is a voluntary program, but in which all the fractionaters who make therapeutic injectable product insist that only QPP plasma be used.

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Specifically, this requires that the plasma donor collection centers be inspected for certain facility standards, for location standards, quality assurance standards, and also the viral marker rates are monitored throughout the industry and those centers that are beyond a certainly limit are given a period of time to correct that or to relocate their facility.

Very important to this effort is the applicant/qualified donor program, and under this, all of our donors are considered to be applicant donors when they first appear if they have not donated within the last six months. After their first donation, they must come back for a second donation, and everything needs to be satisfactory for both those donations before they are qualified donors and their product can be shipped for injectable product.

There is also a 60-day inventory hold on all product to allow for any post-donation information or any seroconversions information to allow us to pull product that should not be fractionated.

Finally, just to remind everyone that the final product is treated to inactivate virus.

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[Slide.]

Let me review what happens to the plasma donor when he or she first comes in to donate, which is quite different than in the whole blood situation. I will use our own company as an example, although there are some variations within the industry.

But all of our donors see a video presentation to begin with, which is that education and information that was referred to in the prior presentation, so they are presented with the nature of the procedure, why they donate, the patients who benefit, the high risk issues, why it is so important for them to answer truthfully, and a number of other significant issues for them.

After seeing the video, they are checked through the National Donor Deferral Registry to see if they have had a positive viral marker test donating plasma anywhere in the United States since the registry has been established in 1995.

There is also a positive check of identification. All plasma donors must have a permanent address within 125 miles of the donor center.

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There is an opiate screen that is performed to assure that they are not taking heroin or any similar drug, and they have the protein, hematocrit, a urinalysis for protein and sugar, and vital signs taken.

They are then asked all the required high risk questions. In our situation, there is a separate questionnaire, and we require, under QPP, a quiz on the high risk behavior. In our donor centers, they are actually given a written quiz, and then the physician or physician substitute, who does the consent and history and physical, asks oral questions to assure that the individual understands the high risk behavior.

Then, very much different than the situation with whole blood, the informed consent, the initial interview, and a physical examination are done either by a physician or a physician substitute. Under the FDA, physician substitute programs, we can train a nurse or an experienced paramedic to be a physician substitute to do the history and physical. The physician must do the training and must continue to supervise the individual throughout his or her employment.

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This takes about an hour or, jokingly, a little more time than most of us get from our physicians under managed care, so the individual has a fairly exhaustive initial entre into the plasma donor center and into plasma donation.

The obvious question in terms of streamlining is given this investment in getting the information from the donor at the beginning, can we streamline more than we have already when the donor returns.

Plasma donors can donate up to two times per week, and given the setup for plasma donation in the United States, our goal is to get the donor to donate regularly, if not two times a week, preferably once a week or at least two to five times a month, so that we have a donor that we can count on for regular donations and obviously one who we have tested multiple times and whose safety we can feel confident about.

So, given this situation, the FDA has allowed the companies to reduce the number of questions they ask each time, but could one go further?

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Now, I wanted to give you some data on our deferral experience, and I have data from several different sources. The first is from two centers that are in a Middle America location, of 3,685 donors, that were screened, 186 deferrals, and this would include both new and returning donors.

In 51 instances, the donor was back too soon. Donors can donate twice in seven days, but if they are attempting to donate a third time, either because they have forgotten or for whatever reason, they obviously are excluded.

Some donors simply won't stay and leave the center for whatever reason. Twenty-eight were due to their veins, and I am assuming that this is not needle tracks, but unacceptable veins to support the procedure.

Twenty-four were deferred for an unacceptable identification, and in our centers, people generally in those geographical areas, have knowledge about things like homeless shelters, halfway houses, addresses that would not constitute an acceptable permanent residential location.

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Now, we do accept students living in dormitories, fraternity houses or military living on base houses.

The protein is measured either through a serum protein electrophoresis every four months or through a refractometer on each donation. If that is unacceptable, the individual is deferred.

Medical issues were 16 of the deferrals, vital signs were 4, 2 were hematocrit, which is obviously less of a problem with plasma donation than with whole blood donation, 1 was a tattoo.

[Slide.]

Now, to move to a somewhat larger company--and we will divide this into temporary and permanent deferrals--they kindly gave me data for this presentation for the first six months of 2000, with 22,257 temporary deferrals, of which the largest number, 5,854, were for health reasons.

The second largest number was the pulse being abnormal, 3,172, and then one that we will kind of keep coming back to it, it has already come up in the whole blood context, the tattoo or piercing, 2,323.

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Hematocrit still does appear as a deferral here at 1,306, 1,132 for blood pressure, and then the urinalysis, protein. This one would refer to individuals who either had an unacceptable blood loss during plasma donation or donated whole blood and too soon to donate plasma. Then, we have our favorite one, the jail, the incarceration, 549 have been incarcerated within the last 12 months for more than 72 hours.

[Slide.]

Drugs or alcohol in the picture, 270 deferrals, 230 for some problem with the arm veins, 47 for hepatitis contact, 42 for intranasal cocaine, which is a 12-month deferral, and 28 for Tegison or one of the other drugs.

So, those are the rundown of the temporary deferrals.

[Slide.]

Now, this is 5,480 donors who were permanently deferred when they attempted to donate at this same company. You will see here 2,108 were for the permanent health reasons, heart conditions or whatever, 341 were high risk donors as judged by the high risk questionnaire.

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The next two related to our National Donor Deferral Registry, were either the results showed them to be in the registry and unacceptable or there were some issues, similar name, similar number, whatever, that required investigation, so they were permanently deferred.

Results on the physical exam were unacceptable for 89, again, there piercing, tattooing, and I believe with this company, if it is over a certain number of tattoos or piercings, it is a permanent deferral, or if they lied about the piercing or tattoo, it is a permanent deferral.

Seventy-eight were because of involvement in the lookback, 44 had a sex partner with risks, and in the plasma, this tends to be a permanent deferral because of some of the fractionater's rules in this area.

[Slide.]

Forty had hepatitis in the past, 15 were in the donor deferral registry, and 9 had sex with a donor who had a reactive viral marker test, and again, due to the rules of the industry, this was a permanent deferral.

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Now, the purpose of showing the data is to indicate that deferrals do occur and the reasons why we have them, but particularly in the context of compensated donors, that despite the fact that these donors would be paid for their donation, there is information elicited either from self-deferral or through answering the questions which does result in the deferral of the donor.

So, this data would suggest that there is utility to the donor questionnaire, the donor questions, and the self-deferral process even in the context of paying for donation.

[Slide.]

This data is somewhat different in that it comes from our specialty centers, 17 centers that collect donors predominantly for rh-immune globulin because they have the D antibody for hepatitis B-immune globulin, because they have the antibody to hepatitis B, or rabies-immune globulin where they are immunized to produce the antibody to rabies, or for diagnostic purposes.

So, in general, these centers do not seek a normal donor off the street, but rather only a donor who has a special characteristic that is in demand, and

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because a large proportion of these donors are older women who have babies with hemolytic disease of the newborn, before rh-immune globulin was available, many of them are donating for rh over and over again, and we have a very low viral marker rate.

299 of the deferrals over the two-month period were for various health reasons, 118 of the donors left, presumably didn't have time to donate at that particular occasion; 56 were deferred because of medicines, 50 were self-excluding, 19 left for reasons unknown, and this may be the individual who is self-deferring after seeing the video or getting some information, recognizing that they will not be eligible; 18 for tattoos or piercing that are unacceptable, 14 for a medical condition, and 7 were in the deferral database.

[Slide.]

Four had a hepatitis history, 4 were identified as high risk in the physical examination, 3 gave a history of male sex with male, 2 tested positive on the opiate testing, 2 others, 2 had an acceptable residence, 1 had a history of intravenous drug use, and 1 had a sex partner that caused the person to be unacceptable.

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So, this gives you a sample of the reasons why people are deferred.

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Since Ms. O'Callaghan has covered this very well, I will quickly go over the post-donation information reports, first, for the same specialty collector, which there were 33 from 2000 to date, and the specialty centers were somewhat higher socioeconomic. We are seeing a higher number of deferrals for the UK travel than perhaps was anticipated for plasma donation as a whole, and this did predominate in this time period.

Then, the next ones are tattoos and piercing, the jail time, unacceptable sex partner, or some health issue.

[Slide.]

Using a different large non-specialty collector with access to their post-donation information, 2000 to date, I would have just guessed from having seen many of these, that this would be over 50 percent, but going along with the data that was presented from FDA, it is almost 50 percent are tattoos or piercings, and the next largest one is quite a big lower, but still up there, is

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a jail term that is unacceptable, the sex partner being unacceptable, the UK travel here is less, the hepatitis history that comes up, male sex with male that emerges, intravenous or intranasal drug, and various others that didn't fit a particular category.

Now, having said all of this, the question is, what do we wind up with as a risk for final product or for viral marker positivity.

[Slide.]

This is the latest data that Barbee Whitaker kindly gave me from ABRA for the first half of 2000, on our confirmed positives per 100,000 of our qualified donors, and this data is used to determine our viral marker acceptability rates for centers.

For HIV, it was 0.87 per 100,000. for HCV, 1.20, and hepatitis B surface antigen, 3.40, and at the current time this still excludes the nucleic acid testing, and we are in the process of putting that into the data.

[Slide.]

Now, this data is somewhat higher than one finds with volunteer donors, and I think the next logical

question is what does that mean in terms of safety of the product.

These conclusions are taken from a paper Simone Glen presented from Westat, in which she looked very carefully at the ABRA data at an earlier time and found that while the incidence rates of HIV, HCV, and HBV virus are higher in plasma donors than in blood donors, that at least in the case of HIV and HCV, where the PCR conversion window is short, the 60-day inventory hold period allows the removal of the majority of the contaminated donations. As a result, the HIV and HCV, the residual risks obtained for plasma donors are similar to those for blood donors.

So, with the 60-day hold, we are able to compensate for some of that additional potential risk, as well, of course, of having the final treatment of the product to remove, attenuate the viruses.

There has also been a paper in the statistical literature from Dr. Glenn Satten, looking at the 60-day hold, and a similar conclusion that it is highly effective, highly cost effective in removing units that

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are potentially positive and improving the safety of the viral load into the final product.

So, on the one hand, we do have slightly higher markers, but on the other hand, the 60-day hold with our particular product is helpful in bringing that down to about the same level.

Nevertheless, I did want to address specifically the issue of whether the fact that compensated donors have higher viral marker rates means that they lie on the interview or that they tend to be less truthful on the interview.

I know this is a widely conclusion that I hear at various committee meetings, but I do want to make the point there is no evidence to support this conclusion, and one can explain the higher marker rates from demographic data alone.

[Slide.]

Again, the same large collector that I showed some deferral data before was kind to give me their donor demographics that they were able to provide, and this shows the age range of the plasma donor population.

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As you can see, it is a much younger age range than one would anticipate for whole blood donors. Thirty-seven percent of the donors, over a third are in the 18 to 24 age classification, and then it goes down from there, the next largest 25 to 29, and so forth.

There are several reasons for this. One is the plasma donation is a somewhat more arduous, difficult procedure than is whole blood donation, and as people get older, they find it somewhat less acceptable unless they are extremely highly motivated like our ladies who have the babies with hemolytic disease of the newborn and are donated into the 60s and 70s.

There also was the problem of the CJD recalls a few years ago, and many fractionaters actually put upper age limits of 55 or so on the donors that they would accept.

Thirdly, as a part of the Quality Plasma Program, many of the centers in lower socioeconomic areas or areas with high drug use have been closed, and many of the new centers that have been opened are centers near college campuses, so college students are constituting an increasing proportion, a high proportion of the donors in

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the plasma industry. There is also some tendency to locate near military bases and use military personnel, as well.

[Slide.]

So, this gives us a very young population and also we have come up with a very strongly male population, about 70-30, and I think whole blood usually runs around 55 percent male, so we have definitely skewed it much higher at the males and a very large proportion are single.

I believe that most of the data would show that with younger males, you would have a population with higher viral marker rates. I don't have any data on racial breakdowns, but I believe that we do, in fact, have a more diverse population than in whole blood, and there are some demographic data there.

Now, I know that it has been a strong force in blood donation to seek donors from low risk groups, but this is not going to high risk groups, this is simply going within the population to the same groups that the whole blood community goes to, but simply skewing it towards the younger, more male population which gives us

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demographically a higher viral marker rate in the population from which we draw, while still keeping to low risk donors.

[Slide.]

So, with all this data put together and in the context of the other discussions, are there some changes that could help us to streamline our procedure and to collect more plasma donors in the United States to meet the need?

One thing that I would like to propose, since we spend so much time and put so much effort into the initial encounter with the donor, the initial examination, and since this is not done by front-line, uncredentialed staff, but rather by physicians or nurses for the most part, could we significantly shorten the interval questions when the donor comes back twice a week.

Keeping in mind that if your whole blood donors in impatient coming every eight weeks with a set of questions, you can imagine what the individuals who come twice a week think about being asked the same thing.

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I have just proposed maybe three questions that could be sufficient - have there been any changes in your health since your last donation with us or any new information you have not previously shared with us? Have you see a physician or visited an emergency room or started new medications? Then, a review of our high risk poster, and is there any reason you should be deferred from donation?

Or if one wants to get away from the yes/no questions and make it open-ended, what changes have occurred in your health since your last donation, what new medications are you taking, what medical visits have you had, and what possible new risk factors have intervened.

So, something that could be very limited and, as Dr. Bianco suggests, very keyed into what has happened in the recent past that might have created a new situation, so that the donor should be deferred.

Then, exclusions that are particularly troublesome to us, the tattoo and piercing one, even though the FDA allows us to accept people if they provide proof that at least piercings were done sterily, many of

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our customers will not accept that and have challenged us to show proof that we know that this certificate they give us indicates it was done sterily, and are insisting that we inspect these facilities, so it is very prevalent in the plasma industry to simply have a 12-month deferral.

Now, it may be that one would want to have the exclusion over a certain number of tattoos and piercings, it becomes a behavioral issue, but at least if individuals with small numbers of tattoos and piercings could be allowed to donate without the 12-month exclusion or with a shorter waiting time, that would be very helpful.

I think the hepatitis history, since we tell everyone who has had a history of hepatitis not to bother to try to donate, if we could remove that and recruit the people based on the information that we have that this is overwhelmingly hepatitis A and represents no risk, that would be helpful.

So, I am grateful that plasma will be considered and I hope that this will result in some streamlining

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that will be useful to us and help us increase our donations while retaining the safety that we have.

[Applause.]

DR. LEE: Thank you, Dr. Simon.

Before we embark on our next topic, I would just like to make a comment about the handouts for speaker presentations that you do not have. There are a few handouts that should be in your packet, but it is not complete. Those will be made available through the CBER web site, and the exact web site should be: www.fda.gov.cber/what's new.htm. For the handouts that you are missing, please look at that web site for complete overview of the workshop.

Now we turn out attention from the role of the questionnaire to a related key topic, which is the actual screening methods themselves.

To begin our discussion, we will hear from Dr. Ron Gilcher, President and CEO of the Sylvan-Goldman Center of the Oklahoma Blood Institute.

Dr. Gilcher.

SCREENING METHODOLOGIES

Emerging Technologies for Donor Screening

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DR. GILCHER: It is a pleasure to be here. I am really going to deliver two talks this morning. The first is a brief talk on which I have a select set of slides, and then the second portion of the talk is actually directly on the computer-assisted donor screening.

[Slide.]

When one looks at donor screening, there really are four parts to it. We are specifically today focusing on the donor history, but a number of the speakers have already addressed the issues of pre-donation information, and I will talk a little bit more about that, donor registration, getting the positive identification, capturing demographic information, and, of course, the donor history where the questions are read and answered or asked as well as then answered, and the purpose here is protecting the donor and the potential recipient. I want to address that in particular.

Then, the donor physical exam with the temperature, pulse, blood pressure, hemoglobin measurement, we have been talking about that as a

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deferral, and one of the major deferral reasons, but that is really not part of the donor history question.

[Slide.]

Now, in addressing the donor screening objectives, what we all have heard and said for years is that we want to protect the donor, and we want to protect the recipient, and that is certainly most important and clearly obvious, but I believe that with the new donor history screening technologies, that we should be attempting to do other things, and that is, trying to retain the donor for the future, minimizing the psychological impact of deferral, and we have already heard about that this morning, and there is no question as we have looked at that in our own system. Once we defer a donor, it is very hard to bring that donor back.

So, we have attempted to modify deferrals in certain situations. For example, an individual exposed to malaria, in our system, cannot donate red cells, cannot donate platelets, but can be accepted as a plasma donor. Attempting then to minimize the psychological impact of deferral, providing recognition at the time of the donation, and that is really training your staff, and

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that is a one-on-one process, providing benefits to the donor, pointing out to them that their donor screening is, in fact, a benefit to them in identifying their blood pressure, et cetera, educating the donor on social responsibility, and then, last but not least, it is very important that this process be rapid and thorough.

Clearly, one of the objections that all blood centers get from their donors is that the donor screening process takes too long.

[Slide.]

The donor questionnaire, it has to be understood by the donor, and a little earlier this morning I addressed the issue of why all the questions, and this is a brochure which we have had in place for a number of years. It was a thought that came out of a donor focus group and then was designed by the head of our recruitment department, and has been, I would say, moderately successful in our system.

It explains why we ask the questions, not what the answers to the questions are, and we believe enhances the safety.

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The donor questionnaire should not intimidate nor embarrass the donor, and what we have found is that in some situations, the person asking the question actually creates an embarrassing situation for the donor. That is one of the clear-cut advantages as we are going to see of the computer-assisted donor screening.

The donor questionnaire requires honest answers, and that is really at least in part due to the method of administration and the importance assigned to it by the blood center.

[Slide.]

When we look at the emerging technologies--and that is really what I was asked to talk on, and I do want to point out that I have very limited experience at this point in the use of the computer-assisted donor screening and really am not the person to be talking about this, there are others in the country who have done more of this than we have. We are just really getting started, but we have done some Internet applications, are in the process of doing those.

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So, I see both the computerized donor history questionnaire and the Internet applications as the two important emerging technologies.

The second part of my talk, I am going to go into detail, on the computerized donor screening, uses the touch screen CRT with earphones. It allows visual and auditory asking of the donor history questions and capturing answers, and then ultimately, with the potential for direct input into the data bank. We see that as being extremely important in reducing errors in capturing data.

The Internet applications, we are in the process of putting "Why all the Questions" onto our web site. We currently are having a test mode and intend to launch this on or about--it was supposed to be launched on October 1st, but will be launched now on November 1st--by putting in proper information on your identity into our system, you will be able to go on to our Internet or onto the web site of OBI, and there will be a new icon that says "Donor Test Data," and you can log onto that, and you will be able to get your blood type, your cholesterol, and interestingly, we are adding ALT on

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there, and we will be able to capture 10 donations, so when you reach donation 11, number 1 will phase out, but there will be 10 consecutive donations on the Internet or on the web site.

We want to use this as a way of trying to really educate our donors to use the web site, and then ultimately, use the "Why all the Questions," and ultimately, the donor registration form itself will be on the Internet, and working with the FDA, we think that it will be possible to actually, in the future, have donors fill out their questionnaire on the Internet and then essentially e-mail that in. We will know exactly when they did it, so that it will be on the day of donation.

[Slide.]

Now, with the computerized donor history automated system--I am going to talk about this at the end a little bit--expensive equipment, I think that is going to be one of the potential drawbacks, and we have to face that issue, that it is going to be more expensive to have this kind of hardware and software available.

In looking at the cost, each station, as we set it up, will cost about $1,500. That will be for the PC,

[--- Unable To Translate Box ---]

for the printer, and for the touch screen. So, each donor station or donor screening station will be an investment on our part of about $1,500.

There will be a server that costs about $5,000 to manage the system, as well, and there will be other costs related to the use of the software, which I will address later.

This will offer better privacy, the donor can see and hear the questions. At our center, in fact, I will be the physician who will be asking the questions. I will show you that in a moment. It will reduce the errors of data transfer from the donor registration form to the main computer once that is a direct link.

We are anticipating that it will reduce the total screening time, since that is a major issue, and data that I am going to show you, not from our own, is that this will promote honesty of the donor. Certainly, this promotes uniformity and standardization. Those are I think really the key features of the computer-assisted donor screening.

[Slide.]

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Now, in talking about Internet applications, by 2002 or 2003, this is the most recent data, is that about 75 percent of what I will call the adult and maybe even the non-adult population in the U.S. will access the Internet. Having the donor registration form available on our web site, with that, as I said, "Why all the Questions," educates the donors, and this will help to reduce errors in interpretation of questions.

It also gives the donor time to think about whether they should be there or they shouldn't be there. That has been a mixed issue in the past. We want donors to self-defer when it is very clear that they shouldn't be donating. On the other hand, what we don't want are donors to self-defer when it isn't clear, and that is why we have designed "Why all the Questions."

Using positive I.D. techniques may allow completion, as I said earlier, of the donor registration form at the person's home, and then e-mailing it to the blood center, and we will know exactly when that occurred.

Then, as I said, we are getting ready to launch the donor's laboratory data being made available to them

[--- Unable To Translate Box ---]

through our web site, and hopefully, this will have donors using our web site more in the future.

[Slide.]

Now, this is the second talk, and this is what I think you have been waiting for, and that is the computer-assisted donor screening technology. I must tell you here that this is not my own word or OBI's work. This is work that has come from others, as you will see.

[Slide.]

Here is a picture of one of the CRTs with a touch screen, so that the donor, with the earphones on, in a private enclosure, can hear the questions and see the questions, and then touch the screen with their answer.

[Slide.]

This is interesting, and this was reported back in 1998 in a newspaper article, that teens admit behavior to computers that they will not admit to a live screener.

[Slide.]

That is seen here. If you look at a SAQ, a self-administered questionnaire, which is here, and then the audio computerized-assisted self interview here, if

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you look at the difference in crack cocaine, almost twice as many donors telling the computer, male to male sex, much higher, about almost four times higher, you can see the ratios here.

Use of IV drugs, street drugs, again, significantly higher. Paid for sex, sex with an IV drug user, quite a much higher ratio, 13.8 times. Sex with a prostitute.

What this I think tells us, if it is true, if it is true, is that individuals will respond with greater honesty to the computer-assisted screening as opposed to a direct interview with the nurse or with the phlebotomist.

[Slide.]

This is the original test system that was set up at Hoxworth. In one way it is kind of a shame that Dr. Tom Zuck couldn't be here to talk about this, because he really has done a lot more with this in the early phase.

At the Hoxworth Blood Center, Dr. Carey was the individual who was in a sense asking the questions of the donors, and you can see the question, the person asking the question, and then a picture of somebody self-

[--- Unable To Translate Box ---]

injecting drugs, again, trying to create the picture to the donor, so that they will really fully understand and answer honestly.

[Slide.]

I think this is important, as well, and again this comes out of the Hoxworth data, is that if you look at the green, this is agree or prefer the computer, the purple is neutral, and the gray over here is disagree, that is, the donors here preferred the nurse.

If you take the neutral and add it to the agree or prefer the computer, it clearly outweighs all of the situations where the donor preferred the nurse. For example, truthfulness, privacy, time satisfaction, and clarity.

[Slide.]

Then, looking at repeat donors and whether they would really prefer this system, again, not as many of the donors preferred the system, but it still exceeded those who preferred the nurse. Of course, you have a much larger donor group that is indifferent, so they could go either way, but if you add these two together, again, it would certainly appear--and this is not our own

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data, again, I want to emphasize--that the computer-assisted screening technique would be acceptable or preferred by the donors.

[Slide.]

Looking at the summary of the benefits which are to be proven--and that was a Phase I study, the Phase II study is really going to be done by three blood centers, one of which is the Oklahoma Blood Institute, and I will show you those three centers in a moment--but starting at the bottom, from the standpoint of safety, there is standardization, the complete medical history forms, not transpositions, no typos, greater than 60 percent fewer reportable errors, that is what the data so far has shown, more honest and accurate responses.

Hopefully, at the customer point of view, that is the donor, that there will be greater satisfaction, and ultimately, to the blood center, lower costs.

I have told you already what the cost of the hardware is, and I will tell you in a moment what the cost of the software is, but we anticipate by looking at our own cost data, that it will reduce our cost by about $1.50 per donor, that is, per donation. That, we believe

[--- Unable To Translate Box ---]

will offset the costs of the hardware and the use of the software, the cost of the software.

[Slide.]

Phase I was the work that was really done at the Hoxworth Blood Center, and then Phase II is where we are now, incorporating the AABB uniform donor history questionnaire and the modifications that will come out with the new questionnaire onto the Internet-based of the computer-assisted system.

Ultimately, really going to where we would have a paperless system, and then capture the data into the computer, and then at some point in the future, allowing the computer to make the decisions. Now, understand that at this point, the computer is not making the decision, the decision is made by the nurse or the phlebotomist at the donor screening site, who will review the questionnaire as it is finished on the computer by the donor.

[Slide.]

In the Phase II study that is going to start now, and this is really the work of Dr. Paul Cumming and the three blood center directors are Dr. Dickey at

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Bonfils, myself at Oklahoma, and Dr. Lou Katz at the Mississippi Valley Regional Blood Center, and we are the three blood centers that are setting up the computer-assisted system of which I am showing you now.

[Slide.]

There is a slightly younger picture of me, and more handsome I might say.

And have you for any reason been deferred to refused as a blood donor or told not to donate blood? And the picture, somebody looking dejected and rejected.

[Slide.]

Here is Dr. Dickey again asking another question, basically the same one that we saw that Dr. Carey had used at the Hoxworth Blood Center.

[Slide.]

Interestingly, at the Mississippi Valley Regional Blood Center, the decision there is to use a nurse, Laurie Rogenski, to really ask the questions, and you can see the picture here, which I think some of us may think is a little bit more than what we should show some of our donors, but I think it makes the point at least in female donors, "In the past 12 months, have you

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had sex with a male who has had sex, even once, since 1977 with another male?"

[Slide.]

This just simply points out the touch screen where the donor can come on, they touch the screen, the question comes up, and then they can indicate their answer, and they can go back if they have a question. They can actually elicit an interviewer to help them if there is an issue, or they can go on to the next question.

[Slide.]

Then, there is a point where the staff will review this, and this just simply shows the donors that have been screened.

[Slide.]

The same on this one.

[Slide.]

Here is how the questions are answered. Where there is a dark blue, like as you see right here, it says that this question needs review by the phlebotomist. If there is a red, it says that the answer, the response was aberrant, and these, of course, are acceptable.

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[Slide.]

The same thing that we see here.

[Slide.]

Here is the uniform questionnaire, and that will be incorporated, so that all three blood centers will essentially use exactly the same questionnaire, and that will be modified to fit the uniform donor questionnaire.

[Slide.]

The summary slide, and then I want to talk a little bit more about cost data because Joy asked me if I would do that.

Again, there are two emerging technologies. One is the Internet, and we are trying to maximize the use of the Internet to do all of these things, and then, of course, the computer-assisted automated donor screening.

We believe that this will result in faster screening. It did not at Hoxworth, if you look at their data, and there were some special reasons for that, but we believe that it will reduce our donor screening time by somewhere in the range of two to five minutes.

We are hoping based on the data that has been accumulated that there will be more accurate and honest

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answers, and then ultimately, there will be fewer transcription errors, and I think that will be very important to the FDA, as well.

Better donor recognition. That is one of the things that we want to build into this, as I said earlier, better donor recognition, better donor retention. All of us are fighting hard for donors. Then, fewer unnecessary donor deferrals, and then Number 7 in here should really be cost.

Let me add a little bit about cost because again, Dr. Fridey asked me to make some additional remarks about the cost. I have prepared a summary for those of you who are interested.

The software, the up-front cost of using the software is going to run about 30 cents per donor. Let's take a 100,000-unit center. There would be an up-front cost of about $30,000.

Then, there is a use fee for the software, and this is typical of all companies that have software, and that will run about $1.00 per donation, so the initial cost of, let's say, for 100,000 donation center would be

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$30,000, but that is a one-time charge. Then, the continued use charge would be about $1.00 per donation.

The hardware costs, remember a single server that will cost us about $5,000 for that server to run the system, and then interface ultimately with our mainframe, and then each workstation, which will be $1,500, about 400 is the touch screen, 800 for the PC, and 300 for the printer.

Now, what about the savings? We believe that the labor savings and then the data input savings at our center will amount to about $1.50 per donation, so essentially, it is going to become a wash, but then when we look at safety from the standpoint of error reduction, and a more accurate donor history, we believe that that is where the real payoff will be for us.

Then, ultimately, in the future, where we will have a paperless system, and also where the computer can actually be making decisions--it will not be doing that initially--where it can be making decisions at a later point in time, might even further increase the accuracy of the system.

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With that I will stop and I will be available for questions later. Thank you.

[Applause.]

DR. LEE: Thank you, Dr. Gilcher, for that very interesting discussion.

To continue the discussion on the topic of screening methodologies, we will now hear from Martha Wells from CBER, on the topic of Insights from the AIR Project.

She has served as the regulatory scientist in the Human Tissue Staff, Office of Blood Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration. Her responsibilities include participation in the program's regulatory and policy agenda concerning human tissue for transplantation.

Relevant to this workshop, she acted as the project officer for the AIR contract from 1991 through 1994.

Martha Wells.

Insights from the AIR Project

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MS. WELLS: I was just told to expedite this as we are running a little late as far as lunch. I didn't intend to get into a lot of the details on this study, but I would like to give you some of the main points of what FDA found from a contract study that we did back through 1994.

[Slide.]

The contract focused on some of the issues that have already been discussed today concerning the computer-assisted interview process. It focused on using an abbreviated questionnaire for repeat donors, and although I won't talk about it much today, it also had a component where it developed a modular training program for health historians, which was thought to be an important part of the donation process.

I will also talk more about Blood Products Advisory Committee review of this contract. This was done twice back in 1993 and again in 1994.

[Slide.]

The name of the contract was Increasing the Safety of the Blood Supply by Screening donors More Effectively. It was contracted to the American

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Institutes for Research who are located here in Washington, D.C. It was initially a two-year contract, which was extended to three years, and it was basically on a different level, but it was a follow up to a previous AIR study that FDA contracted for, titled Intercepting Potential Blood Donors at Risk for AIDS or Other Infectious Diseases.

The total cost of this contract by the time it was finished was approximately $1.6 million. The computer study, the field study of the computer-assisted part of it, ended up being at three sites. It was initially proposed to be for two blood center sites. There was interest from the plasma industry, so it was extended to also testing at a plasma site.

The training modules, there were five of those, and I won't go into those, were also tested at two sites with approximately 88 participants.

[Slide.]

The goal of the study was to improve donor screening by developing a new process that addresses the distinct needs of the first-time donors, repeat donors, and blood center staff.

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As I said, there is two main components, a streamlined and simplified donor screening process and the training program. Throughout the contract we had project consultants from various groups including ABRA, CDC, ARC, AABB, CCBC, and the Army, some of which of you are here in the audience today.

[Slide.]

For the new donation process, this was a total package, it wasn't just the computer-assisted part. It included a pre-donation card which had simple graphics and simple text to hopefully get the interest of the donors and to make the explanations of the process more clear.

The donor computer interview was much like what was discussed by previous speakers that has been implemented since that time. It is an interactive touch screen. There was an audio presentation with headphones. This was to hopefully help donors that might have problems with English.

First-time donors, all the required medical and behavioral questions were required, and there was also an

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educational true/false section of the interview that was included to help comprehension.

The repeat donors, there was an abbreviated version. This version was approximately two-thirds the number of questions for the first-time donors. The rationale for doing this was one of the rationales that was proposed earlier today, that the donors were asked, "Since the last time you have given blood, have you been to see a doctor or other health care professional?" Thereafter, all the questions on major illnesses and other issues that would have certainly caused that donor to see a health care professional were then deleted.

Now, of course, if the donor replied that they had seen it, they would be subsequently questioned about that when they see the health historian after the process.

The donor screener system, this was specifically for the health historian. It included a lot of background library information on diseases and other things that they might refer to if they had specific questions, and it was specifically for them to review the

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interview, see if there is questions that needed to be followed up on.

Then, there was also a post-donation information which was given to the donor after the process.

[Slide.]

As far as the testing of the system for this study, it was determined that there would be a control condition where donors would go through the process that the donor center had in place.

There was an Experimental Condition No. 1, where they would complete the new donor processing system and then do the current system, and then Experimental Condition No. 2 where this was reversed. This was done for this study to ensure that the blood would be considered safe and would be able to be used according to FDA regulation for transfusion and due to liability issues within the centers.

[Slide.]

As far as the number of participants in the study, as you can see here, in the experimental condition for whole blood centers, there were 1,715, in plasma centers there were 753. In the control conditions, there

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were more, 2,905 for whole blood and 1,642 for plasma, for a total of 7,015.

[Slide.]

Other statistics for the study for first-time and repeat donors, as you can see here, there was a City A and a City B for blood donors, which makes the third groupings the totals.

You can see that for blood and for plasma, there was at least two or three times as many repeat donors that participated in the study as there were first-time donors.

[Slide.]

The process was evaluated in many different ways, and I won't go into those. Many of those have to do with behavioral, donor attention, donor attitudes towards each of the processes, and whether it was thought that it would increase screening accuracy.

Donor's preferences for one of the system or not, one of the results was that donors did prefer the computer-assisted process rather than face to face with an interviewer. It also evaluated the variation in

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revealing risk behaviors and efficiency in time completed.

[Slide.]

One of the issues that the evaluation focused on was to see whether there was any difference in the percent deferrals. Now, on this chart, what you see is for first-time donors. Whether they were in the experimental or the control conditions, there wasn't much difference. It was 15 to 16 percent deferrals.

For repeat donors, it was reduced significantly, but again there wasn't that much difference between the two, the experimental and the controls.

One of the interesting things that the study identified or the contractors identified was that the percents of high risk deferrals was significantly differently identified than those that were identified in the control condition. I think this is consistent with the idea that people tend to be more honest when they are dealing with the computer rather than face to face for certain issues.

[Slide.]

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When the study was done, the results were presented to the Blood Products Advisory Committee. It was first presented to the Blood Products Advisory Committee in 1993. At that meeting, the BPAC expressed that they had general enthusiasm for the computer-assisted screening, they thought that it did enhance consistency and was more efficient.

They also endorsed the concept that abbreviated donor histories for repeat donors was advantageous, however, there was not a consensus at that meeting, and a couple of concerns were raised, one of which was that the BPAC thought that they needed more information before they endorsed these programs that were developed under the contract, and they were unclear as to whether they were being asked to recommend this process as a standard or a mandate for adaptation by the industry.

[Slide.]

So, what happened was a subgroup of the BPAC was assembled, about five members, and all the extensive documentation for the study was given to them to evaluate for the next meeting.

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At that meeting in 1994, FDA proposed different questions. These were, "Based on your review"--this is the subgroup--"of the AIR developed materials and the results of the field trial, what is the opinion of the review group members on the quality and usefulness of the donor information cards, the computer-assisted interviews, the abbreviated history for repeat donors, and the health historian training program?"

[Slide.]

Another question to them was, "What additional steps, if any, do you recommend that blood centers take if they opt to implement these materials? If additional studies are recommended, what specific questions should be addressed and by what means? Who should do these studies?"

[Slide.]

FDA also stated a position on what they thought of the materials that were developed by this contract study. These were that FDA endorsed utilization of the AIR materials subject to the following conditions: The information content of the donor card and donor interview should be consistent with current FDA recommendations and

regulations. Changes from the current SOPs should be submitted to CBER for review and approval.

The software systems should be validated to insure that they meet design specifications according to FDA regulations and are consistent with current guidance.

[Slide.]

Other parts of the FDA position include that the training materials for health historians should be utilized in the context of a QA program and be consistent with FDA guidance. Technical and regulatory information should be updated as needed.

An abbreviated history for repeat donors may be used whether or not it is utilized in a computer-assisted interview. Changes from the current blood center SOP again should be submitted to CBER for review and approval.

[Slide.]

So, at the March 1994 BPAC, each of the subgroup members got up and told what they thought they had learned by reviewing more extensive information. Again, it was a lot more extensive information. The first time we went to BPAC, we gave them a 44-page summary. The

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actual documentation of the data and the programs was I would say probably about six inches thick and contained a lot of information for them to go through.

Anyway, at this BPAC, the review groups agreed on the utility of the study and they endorsed the materials developed. The BPAC itself, the total BPAC then unanimously endorsed the FDA position and the bottom line at that time then is that the use of a validated computer system was seen as to be okay, and the use of an abbreviated screening for repeat donors was thought to be okay.

The information for the programs, et cetera, the data, I think can still be obtained by the public. It was given to what we call the National Technical Information Service, and you can purchase it for service costs, I think, if you are still interested in some of the information that was provided under this contract.

Thank you.

[Applause.]

DR. LEE: Thank you, Martha.

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As before, if all the speakers, the presenters from the previous session could come down to the panel, we will begin our question and answer period.

The panel is now open for questions. Go ahead, Dr. Bianco.

Questions/Answers

DR. BIANCO: Those were very nice presentations, but I would like to direct one to Martha. This was a beautiful study, beautiful program, lots of answers. Why do you think nobody implemented it?

MS. WELLS: The AIR study had certainly some technical problems. The issue of having to go through both of the conditions per se certainly confounded the randomization of the study. As to why it has not been used, to be honest, I haven't been following what has been used or what has been developed.

Some of the information that was by the other previous studies seems very similar, certainly more updated and more sophisticated than what was developed under the AIR study, but I think what it did was it provided some good background information that FDA could use to then go ahead and review and approve other systems

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that were on the same idea. So, again, I don't have that answer.

DR. GILCHER: Celso, I think maybe its time hadn't quite come, so to speak, and its time has come, especially when you look at the potential for integrating Internet-based applications.

I mean this whole computer-assisted concept could actually be done over the Internet with the donor doing it at their home and the information coming in to the donor center, and obviously, all of that has to be worked out, but we see at our blood center the integration with the Internet of these two applications, bringing them together, that it really opens up a lot of doors to I think really improve the safety of what we are doing and the accuracy, clearly the accuracy.

I think everybody is focusing on error reduction, and I think this system is going to markedly reduce errors.

DR. LEE: Dr. Epstein.

DR. EPSTEIN: I just wanted to add a comment on Celso's question. My recollection is that although the AIR study developed software, that it was not readily

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transferable to other centers, and so centers that wished to implement it were stuck with the problem that they would have to do their own software development, you know, hardware and software. So, there was a daunting cost element, as well as labor.

I think that part of the success that was seen was that NHLBI--and correct me if I am wrong, Paul--did fund a grant to develop and implement its system. So, I think there was a barrier in that we had approval in concept, that we created a clear pathway because we didn't expect validation of outcome measures by centers that submitted new SOPs, only validation that the system did what it was designed to do in terms of delivering certain information and capturing certain responses.

So, we made a great deal of progress at that level, but again the users were stuck with having to build their systems locally. I think that was the biggest barrier.

DR. LEE: Dr. Fridey.

DR. FRIDEY: If I could just make a quick comment and then maybe ask Ron to respond. Besides the safety, I had asked Ron to address the financial issues

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because I think even today, the up-front costs do frighten many blood centers in discussions that I have had with some people, so I think it is important to emphasize what this does for them, because of the improved accuracy, you have fewer donors calling back to give subsequent information, less rework, fewer discarded units.

That addresses the blood availability issue and some labor savings, so I think that there has to be a pairing off of the savings and the safety issue when we are talking about the implementation and costs of these programs.

Can you talk a little bit, Ron, about how long a period of time it will take you to recover your costs were you to implement this system? You talked to the savings per donation, but how long would it take for your return on that investment?

DR. GILCHER: I have a CFO who looks at everything with a real fine-toothed comb these days, and I think what we are really looking at is that we think that it is going to take about two or three years for us to break even because again, what I said, it is going to

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be about a dollar and a half savings, at least that is our estimated savings per donation, with a cost of about $1.30 per donation at least in the first year, that's 30 cents per donation plus the dollar for each donation, but that 30 cents goes away because that is an up-front cost, $30,000 for a 100,000-unit center. In our case, it would be 150,000-plus, so it would be about 45,000 up-front for the use of the software.

So, over time, we think in about two years, we should break even with this. Now, I am not putting any measure on the safety, which I think is very important, and I think with reduction in having to review all the post-donation information that comes in, and so forth, there is going to be additional savings, but we can't measure that at this point.

DR. LEE: Dr. Chamberland.

DR. CHAMBERLAND: Mary Chamberland, CDC. A question for Ron Gilcher.

I may have missed it, but currently in your Phase II, what role does the health historian play in the process? Does the health historian, for example, get a quick printout or readout of the Q and A's that have been

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done via the touch screen? Is the health historian only involved when there is clarification needed, or, for example, in some of the questions--I am thinking of the malaria question--some of them are a little open-ended, and you might need to probe for specific countries of travel, et cetera?

DR. GILCHER: The end result is still that a hard copy will be printed out, and that will be reviewed by the health historian. If the individual has a question during the process of doing the screening, they can indicate that that is a question, that that question is a question that they don't understand in some way, and then they can ask for help in interpretation of the question.

So, in the final analysis, at least at this point, the health historian is the person who makes the decision. They are going to review the donor questionnaire, they are going to get a printout, and then they are going to discuss that with the donor if there is any questions that are in question.

One of the nice features is that there is no way that a donor cannot answer a question, and as good as all

blood centers think they are, and we think we are good and want to be, periodically, we miss a question, and it is missed and then we discover it later on.

That won't happen here. There is no way that the person can get through the system without answering the question.

DR. LEE: Jan Sigman.

MS. SIGMAN: Jan Sigman, Navy Blood Program Office.

Dr. Gilcher, with your program, we know that sometimes people get confused when they read questions. Do you have an opportunity to go back and change your answers based on, let's say, a subsequent question? Do the donors get a chance to go back and forth between questions, or is that a possibility that they may get deferred earlier than you would really expect?

DR. GILCHER: No, they will have a chance to go back and change a question.

MS. SIGMAN: The other thing that I would like to ask is that many of us have computerized surveys on telephones all the time that we get very angry at, and hang up very quickly. I don't mean to be the person

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looking at the glass and calling it half-full, but when I looked at your slide that showed the indifference after the first donation, I thought that you could also add the indifference to the nurses and you could say they prefer the other way from what you said.

I was wondering if you think that after several donations, and when you have, let's say, a career donor in hand, that they are going to prefer a human touch more than a computer because we all know that donations sometimes become a social event for these donors, as well as an altruistic donation.

DR. GILCHER: First of all, let me tell you that that is not our data. That data is data that came out of Hoxworth. We don't have any data at this point. In about a year we will have data.

I think a lot of this depends on how we at the management level present this to our staff in a very positive manner, so that the staff conveys that in a positive manner to the donor. I think that there was some negativism at least in the first phase, as I understand it from talking to some of the individuals

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involved with the staff, and if the staff conveys something negative, then, the results may not be as good.

What I am hoping is that with our staff wanting to do this, and starting out, at least we are going to do this at fixed sites first, so by definition, we are going to be doing repeat donors in the first phase of this, so they will tell us the truth about how they feel about this.

As far as the personal touch, because our fixed sites do a lot of apheresis, there is a lot of one-on-one that goes on during the donation process itself, and if you think about it, most of the one-on-one isn't really during the screening, it is during the donation process, if you see what I am driving at.

MS. SIGMAN: I worked here at NIH for about 21 years with donors and pheresis, and I have to tell you that we do a lot of one-on-one on the screening process in discussion with return donors because we had about 65 percent repeat donors.

Many of them did, in fact, talk to us on the screening process about places they have been and different medications, and stuff like that, so it was a

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great deal of one-on-one with the donors here at NIH. Obviously, that is anecdotal, but I just was curious with that because again, a lot of our donors come in socially, and they come in for the personal touch and the return warm fuzzies they get from that.

I guess that when I was listening to your presentation, I guess since it was Hoxworth's, I wasn't sure where the persons would first intercede in this particular process.

Would it be coming in the donor room and getting their donor literature or would it be starting from the beginning when they walk in the donor room, they would come in to a computer that they turn on and start to say, just like in, I mean hair cuttery, you go in and you have to type in your own name, and stuff like that?

What would be the process that you would envision in the donor center, that they would be first introduced into the donor room, then, the literature, and then go to a computer, or how would you perceive that or how are you going to do it?

DR. GILCHER: In our centers, the donor comes in, let's talk about a fixed site. They come in, they

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sign in. That gives us a written name or printed name, and a date and time. The receptionist at that point then captures a piece of information, Social Security number plus name and birth date. That goes into the computer as to identifiers and brings up the donor on the computer, and then at that point in our system currently, we print a donor registration form.

It will be at that point that when they put that information into the computer at the registration site, that it will go to the workstation, so that the individual will then go to the workstation, they will be told about what is going on, so the first time is going to be more difficult, but once they go through the process, and we will measure that to see--because these are going to be repeat donors, in fact, in our system these are frequent repeat, and our definition of a frequent repeat donor is a donor who makes at least four donations a year in our system.

So, these are the donors that we will be looking at to gather information.

DR. LEE: Two more questions.

DR. WHITAKER: Barbee Whitaker with ABRA.

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I am interested in Dr. Gilcher's proposal to use the Internet for filling out the DHR, and I wonder how you are going to assure that the person who fills out the form and sends it in via e-mail is actually the person who comes in to donate.

DR. GILCHER: There is no way to be absolutely sure, but if we use certain pieces of identifiers, I am thinking about the information that I put in when I go into my--like Fidelity Investments, I have investments in Fidelity and I have to put in certain information.

We would be capturing that information back from the donor. We would have that information, and then we would have, of course, the time and the date as they access the site. We don't know exactly how this is going to work yet, but if they then come into the center, we have this information, and we would print that information, print the donor registration form right on-line, and we would have the donor there.

We would again verify through their I.D., and, of course, we are relying on their integrity, of course, that they filled that form out, whether they did it on

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the Internet or they have sat down and filled it out at the blood center.

DR. LEE: Last question, Dr. McCurdy.

DR. McCURDY: Paul McCurdy. This question is for Dr. Simon, and refers to the issue of whether paid donors are more or less truthful than the non-paid donors.

On several occasions I have suggested to members of the plasma industry that we make an effort to use a REDS-like anonymous questionnaire in follow-up of some plasma donors. That has never been taken up. There has been a little bit of discussion here and there.

Is that something that would be helpful in answering the question that you said there was no data for?

DR. SIMON: Yes, I think there definitely is interest among some of us in the industry in pursing this, and we have had some early discussions with yourself and Dr. Nemo. I think the question is should the REDS study be exclusively for whole blood donation or should it include plasma donation, as well.

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I personally would be interested in seeing the plasma industry involved, but how that will work out, I don't know. I think our discussions have been preliminary and we haven't gotten to a point of determining whether that is going to happen or not.

DR. LEE: Dr. Gilcher.

DR. GILCHER: I actually have a related question for you, Toby. Tell me if I interpreted your data incorrectly.

You made the statement that the plasma donation companies are really trying to focus on college students. I mean they have in the past, and they are doing more so. Of course, we are, too, in the volunteer sector, but I believe that you said that there was a higher incidence of positive markers in that younger population.

Did I hear you say that?

DR. SIMON: Yes.

DR. GILCHER: Here, I think is an opportunity because that is not what we see, and we are accessing in a sense the same college students, but we may be getting a different group of the college students than you are.

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Let's say there is 1,000 college students, and we get 500, and you get 500 from the same college, and there is a difference in the incidence of positive viral markers, I think there is something in there that we should be looking at.

DR. SIMON: Let me clarify. It isn't that the particular college students we are drawing have a higher viral marker rate. It is just that the overall plasma donor group is of younger age and more male, and it is a particularly younger age because of the shift largely to college campuses.

Actually, the college campuses have helped us lower our viral marker rates in that these particular donor groups are lower in viral markers than were some of the groups that were drawn in the past.

But when you look overall at all the people that we draw, you have a much lower age and much more greater male predominance, and if you look at that group in the population, you will have a higher rates for some of the markers than you would if it were more balanced agewise.

There has been one study done by a sociologist in Ohio comparing Red Cross donors and plasma donors in a

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college campus population, and although we feel there are a number of problems with his methodology, he showed that from a socioeconomic and other points of view that they were comparable populations. That is the only data we have.

DR. LEE: For all other questions, if you could just simply hold them to a later session, we will have another opportunity for a question and answer period.

At this point, we would like to break for lunch. We shall reconvene for the topic Validation Issues promptly at 1:30. Thank you.

[Whereupon, at 12:35 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

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AFTERNOON PROCEEDINGS

[1:30 p.m.]

DR. LEE: I will reopen the afternoon session of the workshop.

We have heard a lot about screening methodologies, as well as the roles of the donor history questionnaire, and we are now turning our attention to the topic of focus for today, validation issues. We all know that donor questionnaires are important, we know that it is a critical piece of blood safety and availability. What we don't know is how good are these, how can we improve them, and how can we validate these processes.

To hear on this subject, we have Dr. John Boyle, who will speak on the topic of Validating the Questionnaire for Comprehension.

Dr. Boyle is a senior partner of Schulman, Ronca & Bucuvalas, Inc., a national public opinion research firm. He has over 20 years of experience in health care surveys for the Federal Government, universities, non-profits and commercial organization.

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He has directed epidemiological surveys of cancer, asthma, chronic obstructive pulmonary disease, primary immune deficiency diseases and irritable bowel syndrome among many others.

Dr. Boyle.

VALIDATION ISSUES

Validating the Questionnaire for Comprehension

DR. BOYLE: Thank you very much.

[Slide.]

I was asked to talk about validating the questionnaire. Now, one of the issues we will be dealing with here today is what do words mean to people. Well, you will see in this presentation what validating meant to me, but it may not necessarily have meant the same thing to the people who asked me to present.

[Slide.]

I do surveys for a living. In fact, I do surveys for a living and because of my membership on BPAC, I have sort of been drawn into the blood industry. I think many of you are in the blood industry and are trying to find an exit strategy from surveys, but what I am going to tell you is not how to get out, but

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hopefully, some things to think about in terms of making surveys better.

Now, when we think about surveys, we think of several sets of error. There is sampling error where we are dealing with coverage, non-response and sample variance, which has no interest to you because you are not trying to project from a sample to a population.

The portion that you are interested in is what is generally called measurement error, sometimes observation error, and the sources of measurement error are typically the interviewer, the respondent, the instrument, and the mode.

Now we break them up like this, so we can sort of segment the problem and look at the problem and look at the problem, but in point of fact, all four of these sources of error tend to basically interact with each other and produce the results that we will be taking a look at.

[Slide.]

The fundamental issue, if there is nothing else that you take away from this, the fundamental issue is that the meanings of questions are not fixed properties,

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constant over all persons in the population. They are not objective measures. No matter how objective they look, they are not objective measures.

Respondents give additional meaning to the question by their understanding of the intent of the question, the survey and the interviewer. It is a subjective response, and a lot of what you have been hearing today is how you try to make sure the respondent understands the intent and purpose of the survey in order to try to get them to respond in the fashion that you need them to.

Surveys are successful in obtaining true measures when respondents make these attributions in similar ways. In other words, you want the same type of response to the same type of stimulus.

[Slide.]

Now, how inconsistent or how invalid or how nonreproducible are answers to surveys, particularly ones that are viewed as objective? Now, what I am pointing out here is one that we have done--this is not published yet--but this is about as objective as you can get.

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"Has a doctor ever told you that you had hepatitis, ever, hepatitis?"

Then, we went back six months to a year afterwards and asked a subsample of the same people the same question. The good news is most of the cases are on the diagonal, and the other good news for those of us who are basically in the survey estimation business is that the marginal rate of hepatitis is about the same. You know, statistically, it is the same in the two samples.

But out of 55 people who reported at Time A or Time B that a doctor had told them that they had hepatitis, only 44 reported it at both points in time. So, you have got a pretty substantial source of measurement error.

For those of us who are interested in estimating parameters, it is not too bad, because basically, it tends to be uncorrelated and you get the two estimates at both points in time as being about the same, but for those of you who are interested in identifying people with hepatitis, it isn't too good that maybe 20 percent of them are not going to consistently answer that question, and at any given time, 8 to 12 percent are

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going to answer it in the negative although in point of fact, at another point in time, it is the positive. None of these cases are as the result of new cases of hepatitis because we have the date of diagnosis.

[Slide.]

Why do errors happen in surveys? Why do measurement errors occur? We are really looking at issues of validating the questionnaire for comprehension. We are not trying to look for lies, we are looking for other types of problems that cause bad or error responses.

In breaking up the cognitive process of answering questions, which comes out of cognitive psychology, basically, we break it up into five steps - the respondent's encoding of the information, their comprehension of the information, their retrieval of the information from memory, their judgment of the appropriate answer, and their communication of that answer to the respondent.

Now, cognitive psychology isn't new, but its uses in surveys go back only about 20 years, so there is not a ton of data in this area.

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What we know is that, first, look at the properties of words in questionnaires. First, words may have no inherent meaning for the respondent. The respondent may look at the word and have no clue as to what is going on. They will, however, not want to not answer, so they will look for clues in the surrounding answers or in the structure of the question to try to give you an answer.

People, whether they are coming in for blood donation or whether they are answering me on the telephone or in the mail or in person are trying to be cooperative, and they will try to answer your questions even though they may not know the answer.

Words can also be taken to mean different things by different respondents, and words can be taken to mean different things by the same respondent in different contexts.

[Slide.]

Real life issue. I had a client who wanted to include in the survey, in the demographics, some questions about sexual orientation. Okay. We tried to

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dissuade them because of issues of comprehension. They insisted on doing it and sat with me during pretest, and they heard a nice lady, who was asked the question in the demographics, "Are you bisexual?" And she said, "Yes, absolutely. My husband is the only man in my life." The question was taken out of the survey. But that is the problem.

Another thing similar to this is we have had clients who have tried to put in the demographics "Native American," and they heard it in the pretest, "Native American, absolutely, I was born in Texas, my father was born in Texas, I am a Native American."

So, you have to go with words that people understand, and you have to know whether they really truly understand them or what the error rate at least is in the understanding.

[Slide.]

Now, aside from even understanding the word, the question is interpreting the meaning. Here is a very common thing, "weekday," you know. It is used in lots of surveys, but when you actually go out and ask people, when they responded to weekday, what did they mean, well,

the majority said it was Monday through Friday. A third, however, thought it was the full week, Sunday through Saturday, and others had other varying interpretations of this.

Now, "weekday" isn't very complex, but I can give you a stronger case. In one survey, people looked at the meaning of the word "you." Now, the good news was 87 percent interpreted the word "you" to mean you and you alone. The others, however, said "you" meant me and my wife, me or my wife, me and my kids, my family, some even stretched it to be the community.

But the good news is most people tend to use a lot of words in common parlance the same way, but there are problems, and you need to recognize that because when you move on to more complex issues, and one that I have seen up here today is sex, I mean we know people interpret that word differently even in court trials.

I can tell you in other areas, where, for instance, we have done a lot of work in sexual assault, and there are a lot of surveys that ask questions about sexual assault or ask questions about rape, and it is on the National Crime Survey in such a fashion.

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We went out and didn't use the word, but we actually asked a series of questions about what actually constituted that, and the simple fact of the matter is when you ask it that way, you get a much higher reporting than when you put a label on it, because people don't necessarily agree with the label. That is what is terribly important, if you want object information, ask questions as objectively as possible in a way that people can respond in that way.

[Slide.]

Now, here is a result of doing some cognitive testing. We have done a lot of seat belt surveys, and the way the questions are usually asked is, "When driving this vehicle, how often do you wear your shoulder belt or seat belt, do you wear it all the time, most of the time, some of the time, rarely, or never?"

Now, in doing cognitive testing, we discovered that the simple fact of the matter is, is that if you ask people who say that they wear it all the time--and, by the way, the reason it was asked was this didn't match observational studies, which indicated lower rates--so,

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you ask the people who said that they wore it all the time, "When was the last time you didn't wear a belt?"

By the time we did the survey, you can see the results, that 4 percent of the people who say that they wear their seat belts all the time, say, well, the most recent time they didn't wear it was today, 6 percent within the past week, another 4 percent within the past month, and another 4 percent within the past 12 months.

Well, the good news is 71 percent understand it the way it was intended, another 12 percent maybe, because of that "not sure" category, but clearly, close to a fifth didn't understand it, and when they were asked in cognitive testing, so I don't understand, you said all the time, and you said today, they said, "What's the problem?" All the time is the rule. Okay. I put it on as a rule, not as an exception. Did you mean it literally? That is one of the issues, people are looking for are not necessarily clear on what the interpretation of that term is.

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Then, you force them, if they have understood the question and the meaning, to select a response. Now,

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this is sort of illustrative. This is a study that we have done on irritable bowel syndrome, but we asked the same people two sets of questions, and we weren't trying to be tricky because depending upon which criteria you used, you needed different questions.

What we saw was we said, "Is this discomfort or pain relieved by a bowel movement?" Fifty-five percent said "Yes." "How often do you experience relief of pain, discomfort or cramping with or after a bowel movement?" Sixteen percent said "Always." Another 29 percent said "Frequently." It is up to 46 percent. But another 34 percent said "Sometimes."

If you use a "sometimes" criteria, you got 80 percent. If you use a yes/no, you have got 55 percent.

Now, I pose this issue to you. This makes a difference to us in terms of hitting certain criteria, but to you. If you ask questions like "Do you have sex with other men," if you ask sometimes, would it make a difference? Does sometimes mean no, or sometimes mean yes? That is something you have to know to know how good your questions are.

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Now, one issue that concerns me a great deal, because I have had problems with this in surveys all my life, is trying to recall time bound events, and this gets you into the case of have you had sex with other men in the past 12 months, or have you had IV drug use in the past two years, or whatever else you like, you are asking people to give you a time frame.

Now, time bound events are trying to get recall, biographical recall, of events has a series of problems. First, there is the failure to recall the event from the description in the questionnaire. People don't always necessarily get what you are asking about.

There is a failure to distinguish between similar events. What happens I think more commonly is there is a forward telescoping in time of salient important or socially desirable behaviors. When was the last time you helped your kid with his homework? Last night. Okay. There is a backward telescoping of less salient or socially desirable behaviors. You know, when was the last time you had 10 or more drinks in an evening and totaled the car? It has been years.

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However, if you go out and actually have markers, what you will see is, by and large, things that are important and things that are desirable get moved forward in time, so if I ask did this happen in the past year, you know, did you go to church in the past year? Absolutely.

But if I asked you something else that is less socially desirable, it gets pushed back in time. Now, the worst case is when I asked you questions that are socially unacceptable and in some cases criminal, okay, and that has to do with drug surveys.

Whenever I do a drug survey, the answers about have you ever used, usually work fairly well, but when I asked you have you used this in the past 12 months, oh, boy, when you do panels, and you go back and you compare what they said at Time A and what they said at Time B, it is very clear that people are unwilling to disclose close-in events that are threatening or undesirable or whatever, so be very careful about bounding your events if you want an accurate answer.

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Now, communicating the appropriate response. One of the things that you see here--and this is obviously the interactive nature of questioning--that depending upon the race of the interviewer, the response of the respondent varied fairly dramatically for the same sets of questions.

Now, this study was done in the seventies, so maybe the difference wouldn't be as great as now, but if you did it on some other topic that is more relevant, you know, sexual orientation of whatever, I guarantee you, you know, you will see these types of effects.

Now, these are attitudes. We are not interested in attitudes here, we are asking for hard factual information. I will give you an example of something that falls right into that. I saw a survey in which the educational attainment of the respondents in a panel declined over time, and the reason it happened, after going back and doing some analysis, was the people who did the in-person interviews at the first point in time were very good looking, highly educated, highly articulate, and a particular group appears to have raised their educational level, and then when the second group

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of interviews came back, six months later, who just basically looked like slobs. It went back down to what we believe was the pre-level. So, there is an interaction that you have to be aware of.

[Slide.]

There are common concerns about question wording that you should have, whether the respondent understands the word or willing to show ignorance. The respondent may try to simplify a difficult question, so it can be answered--and it looks like you asked some pretty difficult questions--respondents may answer with the spirit of the question rather than the exact words, which means they are answering to the way they see it, not the way necessarily you wrote it.

Parts of long and complex questions may be overlooked, and I can tell you in telephone interviews we know what people tend to hear as the end of the question. Response categories may not fit respondent's experience, so they may alter them to make it work.

Question order may lead respondents to answer questions based upon an unintended context - oh, they

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asked me this, this, this, and now this, what they must want is this.

Then, finally, as you are all concerned about, questionnaire burden may cause respondents to answer without thinking.

[Slide.]

Now, in terms of validating, the only true way to validate, and validation basically in this context means what the question measures is exactly what we intended it, the only way to do it is using measures external to the survey, so either using reverse records checks or forward records checks, or a combination, you begin by knowing who has hepatitis, who has had sex with men, who has a criminal record, and then you ask them the question, and you find out how accurate the responses are, or you do it the other way, you ask them the question, and then on health surveys, you ask for access to medical records in order to validate those things.

Those are the only ways that you can actually truly validate survey questions, and it is very difficult to do that.

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By and large, what we do in validating survey questions is not to truly validate them, but basically, to understand whether or not the meaning and understanding is what was intended, and that is usually done in one-on-one interviews, not focus groups because what you are looking for is do you understand the question, and you don't want to look dumb in front of other people, what do you take off this, and you don't want what anybody else thinks, so you really want to do this one-on-one, you want to use actual forms and questions.

You would like to represent the full range of likely respondents, the smart and the dumb, the shy and the less so. You want to make the mode of administration as similar as possible to the actual survey. You want it conducted by a skilled interviewer, and you want it observed or reported for researchers.

This doesn't mean it has to be done in a central testing facility. It could be done in a private area, and it does have to be a private area, within a blood donation center.

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The main cognitive testing techniques that are used today are concurrent think alouds, where I ask the subject to verbalize their thoughts as they read through the survey questions and as they prepare their answers, and as they answer in verbal probing, where after they have read and answered the questions, I ask them to make explicit what exactly happened in the answering process.

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I will skip that one.

[Slide.]

The concurrent think aloud, the way we would actually administer it, say go ahead and begin the survey, tell me what you are thinking as you read the page, read the question out loud. Now, do you have any special feelings as you read the question? Tell me what you are thinking as you answer the question. If you are not sure what the question means or how best to answer it, just tell me as we go along.

There, we get a picture of how people are thinking through these questions and how they are responding, so we learn about not only their

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interpretation, but their whole answering strategy and choices.

[Slide.]

The verbal probing is actually easier to do, and so it is done more often, and that is, I say, "Now read the question to yourself." Okay, they have finished. "Now, rephrase that question" sometimes without looking at it. So, I can take away with what you took away that question, and I will tell you, you get back some very interesting questions when it is paraphrased.

The next question is what is the real meaning of the question, what are they trying to get at. How would you answer the question in your own words, don't use the category, just tell me how you would answer the thing.

Now, if you had to pick a category, which one would you pick. Now you can compare these two and see what people are actually doing. How would you change that question to make it clearer for people like yourself? Their suggestions may be good clues about how to help somebody at that level to get a clear answer.

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Finally, normally, what you do, particularly in self-administered questionnaires, is you ask them to go back to the questionnaire. You ask them questions about the average person, which ones are they going to have trouble answering, which questions did you really have to guess about, which questions do you think the average person is less likely to answer honestly. Be careful with that one because a lot of people think everybody else answers them dishonestly, but at least it gives you some clue as to where they are thinking, and which questions are asking things that you have already answered elsewhere, because as some of you have already said, that is one of the things that people really react negatively to, "I have already answered that question."

[Slide.]

The primary objectives in donor questionnaire redesign is to make sure respondents understand the question, so they can answer it accurately. Questions and answers are unambiguous, so convenient misunderstandings are minimized. A lot of people don't lie, but you have to ask the question three times to get

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the right answer because if you really don't want to do it, well, they are not really asking that.

In a lot of cases, if we ask basically the same question on a sensitive area a couple of times, the second or third time, you get a lot of reporting you didn't get on the first one.

Finally, make sure the survey intent is consistent with honest and thoughtful reporting, and make sure the respondents understand that. One of the questions that I would raise is do they believe that the surveys that they are doing are confidential.

I can tell you that 25 percent of the American public does not believe the census is confidential, and if you don't believe it is confidential, that may indeed affect your behaviors.

So, that is a quick run-through, and I am sure you will hear more about strategies for trying to make a better questionnaire later this afternoon.

[Applause.]

DR. LEE: Thank you, Dr. Boyle.

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Next, we will hear again from Dr. Williams. He will address part two of the same issue, Validation for Determining Effectiveness of Questions.

Dr. Williams.

Validation for Determining Effectiveness of Questions

DR. WILLIAMS: Thanks again, Jong.

I really enjoyed the last presentation, and it just strikes me as more and more incredible that for a survey instrument that is administered 13 million times a year since 1953, that this has never been done. So, I think that helps provide some direction for us.

In this talk, the word "validation" is used in eh title. In fact, what I am going to talk about is some of the performance parameters of the questionnaire, the data that we don't have, what some of the difficulties are, and some potential strategies for collecting it.

Really, I think the measures we are going to be mostly concerned with are issues of sensitivity, specificity, and predictive accuracy, and I will be referring a lot to the need for a gold standard to define those performance parameters.

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I wanted to make one summary statement sort of defining this problem of how well do the questions detect the type of risk that we want to determine excluding. It ended up sounding like a Woody Allen statement, but I keep it anyway.

The current donor screening is a burdensome patchwork of questions, the individual elements of which, in the absence of data, are viewed as being useless by some and critical by others.

I think for many of the cases, that in fact is the truth, that in the absence of data, there is a lot of opinion and it is just going to be very difficult to work out a common ground for policy decisions.

[Slide.]

How did we get to where we are in terms of the quality of the donor questionnaire? I have heard several individuals say, well, we should evaluate the donor questionnaire process the same way we do a laboratory screen. It's a nice comprehensive way to consider it, but probably not practical.

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Historically, donor qualification receives less attention than laboratory testing for a couple of reasons. One, the science is softer, it is much more difficult to measure outcome measures and performance of a questionnaire process than a laboratory test.

Unlike laboratory tests, which are developed in the commercial sector, there just isn't a big financial driving force behind this process, and the primary cost is really loss and frustration of donors.

Similarly, the regulatory agencies, not only in the United States but in other countries, put a little lower level of review on the question process, and don't hold it to the same performance standard as they do for laboratory screen test licensure, and, in fact, blood centers, if they build into the SOP's, are free to ask questions that other blood centers would not ask, and that certainly would not be the case for a laboratory test.

As Jay I think mentioned earlier, implementation tends to be reactive, sometimes necessarily so, usually with minimal or not validation or standardization of the questioning process. There has been some move towards

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standardizing that from a regulatory standpoint of late, but in the earlier development of questions, there really wasn't any validation or standardization conducted.

Behavioral input is lacking. This is I think a very important point. We have had sociologists and behavioral scientists interacting with the blood field for a number of years, really, no one ever involved on a full-time basis, and as you can see from the quality of the prior talk, really, no high level scrutiny of our questions to see if the comprehension is really there.

Donor loss is largely deemed recoverable. I think the one time that this was really considered was with the UK deferral where HHS really requested data to determine donor loss, so that they could make a balanced policy without crippling availability, and evaluation of the donor qualification process is difficult and, related to that, usually expensive, and therefore it is done minimally, if at all.

[Slide.]

Not that there has been a lack of discussion about the issue. Shown here--I am not going to go through the list--but just largely, since 1990, there

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have been a lot of discussions about the question process, implementation of new questions, discussion of the AIR study, and the ongoing questionnaire, culminating in AABB-sponsored task force on streamlining the blood donor questionnaire, it is a very difficult process.

What I want to do is go through some of the reasons why it is tough to make progress.

[Slide.]

To start off with, to distinguish what I am going to attempt to address from what Dr. Boyle addressed, consider donor qualification as two separate, but certainly not independent, parameters, the first one being the validity of the screening criteria that are used to reduce or eliminate transfusion-transmitted infections.

What I am talking about here is the science, is the content of the question correct to eliminate the risks that you are trying to take out of the blood supply. The second part of that is validity of the screening methodology used to identify and defer donors once specific screening criteria are selected. I would consider that the process itself, the wording of the

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questionnaire, comprehension, and so forth, I think two separate elements, and it might be helpful to consider them separately.

[Slide.]

In terms of making progress, I think we also have a good news/bad news process here. I am not encouraged that approval of a largely modified donor questionnaire in terms of content will be reached without additional supporting data, and I think the data is going to require probably large, well-constructed, somewhat expensive studies, not that we can rule out reformatting the questions using capture questions and things like that, but the actual content, should we be asking questions about hepatitis, I think that is going to be difficult to reach without new data.

The good news side of that is data has been so sparse that evaluation measures are so badly needed that even modest data will probably support new policy.

[Slide.]

The performance measures have already been mentioned, involves validity largely related to whether the question addresses the areas that you really want to

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get at, but in terms of other performance, sensitivity, specificity, and particularly in a donor setting, as mentioned earlier, predictive value, both positive and negative, are particularly important when the prevalence of what you are trying to get at is very low. Those are the two measures where the prevalence of a factor really kick in.

[Slide.]

What I would like to mention here is that in determining each of those four measures, you need to have a gold standard, exactly what are you trying to eliminate. When you think about it, many of our questions have an ambiguous gold standard, and I raise sort of a controversial statement here, that since the reason for risk screening is prevention of post-transfusion infection, donor risk questions are really all based on surrogacy because you are not asking someone in effect can they transmit a post-transfusion infection.

You are asking them questions about behavior which may have put them at risk, and certainly that is the only mechanism we have, but as a result, sometimes

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the gold standard for evaluation purposes can be ambiguous and scientific credibility may be challenged.

I think we have seen some of this in recent discussions of the MSM deferral factor when the current screening question, of course, is behavior since 1977, and I think very legitimately, others raise the issue, well, shouldn't be unprotected sexual contact with multiple partners in the last year, doesn't that make more scientific sense. Yes, it does, it depends what you are trying to measure, what is your gold standard.

[Slide.]

One of the basic principles of epidemiology, and I think it is compounded when you have very rare factors you are trying to measure, that as you raise the sensitivity of a question, it torpedoes the specificity of the question. These two work in opposite directions, and that is one of the problems that we are faced with in trying to make our screening systems as sensitive as possible.

Consider that in evaluating either existing or new questions. Perhaps the best way to look at it would be with a clinical trial, like you would do for a new

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therapeutic. It wouldn't be hard to design. For an existing question, you could simply eliminate it in one arm of the study and measure outcome or donor markers, or something of that fact. For a new question, you could implement it in some centers and not in others. In terms of design, it wouldn't be that difficult.

[Slide.]

However, it doesn't happen in the field, and there are some good reasons why not.

In the therapeutic setting, one of the major components of a clinical trial is the safety of the recipient of that therapy. Since screenee safety is not a negligible issue, donors, if they are deferred, okay, they can no longer donate blood, they have different levels of reaction to that notification message, but in large part it is not a safety issue.

Post-transfusion outcomes are rare, very difficult and expensive to measure. Often, the question of administration takes place because time pressures are present, such as the slide shown earlier about the recognition of post-transfusion AIDS, and the need for question implementation, and probably one of the major

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barriers were you to run a clinical trial, could you imagine using an informed consent process for recipients, that we are running the study, we really don't know whether a question has benefit or not, and would you consent to being in a blinded trial, so that we can determine whether this question is of value. It would just never happen.

So, those are some of the difficulties why the clinical trial process, which could answer some of the questions, just isn't practical in our field.

[Slide.]

Are there other designs? Sure. There aren't a lot of them, but there are some. You can pre-sample first-time donors and get a sample in hand for all deferred donors depending on the staging of the process. When the donor comes in, at least in our system, you have to collect a system for all first-time donors, and then save those when the donor is deferred, and you would thus have a sample for testing which could be linked to the deferral itself.

It could be done anonymously or linked, which would need an informed consent process. It is doable,

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but will the benefit justify the cost and effort that goes into the study, because the outcome measures are so rare, it would be hard to produce compelling data on a study like that.

In response to the question earlier, I mentioned that you could do an interview sampling study of deferred donors. The difficulties with that is for some of the key questions of interest, particularly the risk questions, those deferrals are uncommon, and it would really have to be a large, if not nationwide, study to study something like HIV risk factors, and since you have an enrollment process, there is a lot of potential for bias, and again it would be hard to produce compelling data, but not impossible.

One other way to get at some of these issues is now that we have NAT testing in place, the sequencing of the testing process is really quite rapid. I am sure the donor screeners wouldn't like it, but I think we might have a natural experiment whereby when a donor is found to be positive for something, that one could, in fact, investigate the screening process and see if you could identify where something went wrong.

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It certainly would be a controversial thing to investigate, but it would give additional information about where screening processes do not detect the factors that they should be.

[Slide.]

The evaluation environment is very difficult. With limited exceptions, blood centers have been unable to conduct formal evaluations of processes in a regulated environment. I think some of the early studies with the computerized donor screening system ran into this.

One of the early designs was a crossover study where the donors needed to go through both processes, the standard process and the computer process in order to make use of the blood. Until recently, the FDA did not approve sites simply using the computer screen and allow that blood to be used for patient support.

There has been some flexibility on the issue of late, but that I think sort of emphasizes the fact that formal evaluations or experimentation within a standardized environment just is difficult.

[Slide.]

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From a behavioral science perspective, I mentioned we have had very little behavioral science input. What is known from the HIV researchers in the field unrelated to blood is that information about personal behaviors is inherently difficult to collect, whether it is a general population audience, a risk population, or blood donors.

Response rates tend to be low, missing data is frequent when you use a self-administered questionnaire, and internal inconsistencies are also frequent. There has been a lot of progress in this area, and there is a whole literature now which is emerging using the audio computer-assisted questionnaire instrument. Charles Turner and others are working in that area.

I think that serves as a good model for what might be introduced in our field, as well.

[Slide.]

Some other considerations. The donor forms their own basis for risk assessment. It can be self-denial or, as mentioned earlier, if someone feels that a screening process is politically driven rather than based in science, there could be a lack of respect for policy

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on that basis, and potential donors might just ignore the question.

External factors could prevent correct self-deferral. This is comprehension as measured earlier. I think it is a factor in our screening environment. I don't think it is the overwhelming factor, simply because there is so much pre-donation deferral before the donor ever reaches the sites, and we see on the post-donation questionnaires, we actually see a differential. If the folks are understanding the question on a survey, why did they not understand it on site? There might be some explanations, but we do see that differential.

Other factors are environment, the type of individual doing the screening, the privacy considerations, and so forth. As we see from some of the donors identified in the HIV seropositive study, in some cases, unfortunately, it is just a lack of concern for recipient safety.

It is not a large factor, but you do see that coming through in some donor interviews.

[Slide.]

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You are all aware that NAT testing is upon us. Virtually all blood is now tested for HCV and HIV, and it is closing many windows, but it might open a new window of opportunity for change in some of the other systems.

[Slide.]

I am going end with a series of recommendations. These are just thoughts based on some of these difficulties which might help start us moving toward a streamlined questionnaire.

The first one is to create, for lack of a better word, a living public document to formally define the parameters for each screening question. I think the task force has sort of started on this road in its data collection activities.

Elements would be what exactly is the question designed to capture, what have been previous validation efforts, what is the cost of retention of the question, what would be the cost of removal, what further data are needed and what is the feasibility of that data collection, and what is the regulatory and AABB standards history of the question.

[Slide.]

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Second, initiate a systematic comprehension validation process for current questions. You don't need too many more workshops to recognize that this is needed, and as long as funding can be identified, this can be done.

The Red Cross has a paper coming out in the next issue of Transfusion. We did use focus groups to take a measure of questions that were chief contributors to error and accident reports, and it is a small study, but you can see we did identify some problems, and this is a very doable area of work.

[Slide.]

Recommendation 3, arrive at agency and industry agreement, supporting responsible implementation of new donor qualification measures including design and validation and estimates of impact, also something that is doable right away without more workshops.

[Slide.]

Recommendation 4, investigate new donor screening mechanisms. I won't really go through these since they are being discussed today, but they include

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capture and interval questions, computerized interface, and so forth.

Also, I did mention that donation education is an important factor. We might think about ways to take better advantage of that since that appears to be one of the major deferral factors.

[Slide.]

The second to the last one, strengthen the infrastructure, adequate targeted funding to accomplish the defined needs, programs to attract behavioral scientist professionals into our field, and research structures to facilitate ongoing validation and measurements of the screening process. It could be some smaller version of something like a REDS study, which is just in place to do validation and similar measures as new questions arise.

[Slide.]

Lastly, consider IOM or another independent sponsorship of a forum to talk about an agreed rationale for current and future questions including, quote, "cost considerations and to recommend mechanisms through which

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new screening procedures can be evaluated within the regulated blood collection operation system."

Thank you.

[Applause.]

DR. LEE: Thank you again, Dr. Williams.

We will now turn our attention to the abbreviated questionnaire, and we will now hear from Dr. Linda Chambers of the American Red Cross.

ABBREVIATED QUESTIONNAIRE

Possible Approaches for an Abbreviated Questionnaire for Repeat Donors

DR. CHAMBERS: Thank you for inviting me to share what are going to turn out to be primarily comments from anecdotes, best-guesses, and some independent thoughts of mine on the issue of an abbreviated donor history questionnaire.

[Slide.]

I started putting this together by getting a copy of the current Red Cross questionnaire, and I had a couple of, for me anyway, surprising, sort of first impressions.

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One was that the type is awfully small, and for those of us with mature eyesight, it is very difficult to even physically read some of the questions on the questionnaire currently. There certainly are a lot of them.

Secondly, the questions are complicated, as has been pointed out. Many of them have multiple parameters to them, dates, situations, covariables for those situations, so that the questions are complicated and really unless you have read it three or four times through and know what the issue is at hand, I think it is impossible to comprehend.

There seemed to me to be a lot of re-verification on repeated application of the questionnaire of history that has already been given, and I think that is the crux of the interest in something like an abbreviated questionnaire.

I also noticed that we, at least Red Cross does, and I imagine that other blood centers fall into this same trip, group the questions based on what the blood transfusion issue is as opposed to what the setting would be in normal common parlance.

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For example, we group the questions for CJD, so that the current question reads as follows: Have you or any blood relative had CJD? Have you ever been told that your family is at an increased risk for CJD, or have you had a dura mater transplant during head or brain surgery?

We know those all relate to CJD. What the donor hears is for breakfast this morning, did you have an apple, did you have an orange, or is your mother a registered Republican? I mean to them, they are completely disjointed, and they can't, unless they are a blood banker, understand why we have got those things lumped together, so we don't even do a good job, I think, of putting donors in one setting, we are going to talk about your medications, we are going to talk about your family, we are going to talk about your medical history, and group things that might represent issues for different infectious agents under sort of a common mind-set for the donor.

So, I think there are lots of opportunities even if we never got out of the box and just thought about anything beyond having 40-whatever questions for each one of our donors of doing a better job.

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But with that preface, I would also like to apologize for not getting my materials to you ahead of time. They are out front, they are on the desk. There is a copy of the slides and there is also just a sort of an initial pass at what an abbreviated questionnaire might look like.

[Slide.]

The questions can really be put into two categories very comfortably. The first are things that are today issues, current issues, very recent stuff, and then a whole host of time-linked issues, the "Did you ever" - "Since age 11" - "In the last year" - "Since 1977." I think that is important to make that observation, how many questions. We do have better time-link given the comments about human nature and how time telescopes, shortens or lengthens, depending on the issue at hand in terms of time recollections.

What we do currently, of course, is we obtain those time-related responses and then re-introduce them, re-question, and verify them with every single donor questionnaire, because the question is asked without change, so that the start time is still the same.

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The concept would be that particularly for those time-linked issues, that at some point we would figure that we had documented history, we had heard history, and we had assessed it as being okay, and our only interest with the current questioning would be to update that history for the time interval since the last donation.

[Slide.]

The concept is that this would be for regular donors, and there would obviously need to be some kind of definition for regular. It can't just be repeat donors because people may repeat at two-year intervals or five-year intervals, but for some definition of regular donors, that the questionnaire would be shortened to those current issues like Do you feel well? Do you have an infection? Are you on antibiotics right now? And then updating any of the key time-linked issues since the last donation. So, since the last donation have you..., and then proceed with the questions that are time-linked, but for which the history has already been established, documented, assessed, and found to be okay.

I would like to introduce a third concept, which would be for non-key, if you will, time-linked issues, to

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revisit those other issues through what I am going to call a capture question, that is designed in such a way that it takes advantage of the fact that someone who has already been accepted as a donor, is unlikely to have a positive response and a problem in other areas that would be cause for deferral. I will show you concretely what I mean by that.

[Slide.]

The donation interval has got to be short enough, however you define a regular donor, so that this concept of "Since your last donation," is the time frame that is easily recollected. I think something like 12 months is very reasonable. I don't think we would have to restrict application, for example, to donors who come four times a year or more, because there aren't very many of those, to be honest with you.

You may want to apply in an abbreviated questionnaire only after you have been through the entire questionnaire with a donor for a couple of times, and I think the reasons for that are mostly ones of comprehension.

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Many of the post-donation information problems that are really subsequent donation information problems happen with people who are making their first, second, or third donation, where it is only with the re-reading of the question and an opportunity to kind of mull it in between the donations that they realize that they have reportable information.

Certainly, we are moving quickly to a time when displaying previous responses for verification is feasible. Things can be captured electronically and redisplayed electronically, and so there is an opportunity to present the donor with information that they have given previously, and have them verify it as opposed to eliciting the information for the first time with a repeat of the questionnaire.

[Slide.]

I think that many of the benefits are obvious, but I suspect that there are some secondary benefits that would be interesting to watch for if this were implemented. Certainly, a shorter donor evaluation time is good in terms of cost and staff time to do the procedure.

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It is going to not only be better for the repeat donor, but it is also going to be better for the other donors who are waiting in line behind that repeat donor, so that the effects are not to shorten the time only for the individual donor, but the time in average for all donors.

I think there is a potential for a secondary, what I am going to call "member of the club expedited service reward." When I call Eddie Bauer and I want to order something, and I give them my name, they look it up and they ask me if it is to the same address and do I want to charge it to the same credit card I used last time. That is reinforcement for doing continued business, and I think someone who perceives that they are known to the Red Cross, they are a frequent donor, Red Cross has my number, they got my history, and I am special. I come in and I go through a special expedited service. I get better than average customer service because I am a frequent flyer. It might be a very powerful message in terms of donor recruitment and donor retention.

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Certainly, a shorter questionnaire reduces the potential for clerical and omission errors just of documentation. I think an important part is that it focuses the donor on the changeable responses. Rather than have them distracted with - Since 1977 - Since age 11, et cetera, an old history that has already been reported, verified, evaluated, and found to be acceptable, if their attention can be focused on what are the current and changeable features, then, I think it has the potential for decreasing inaccurate responses, which has the return, of course, for increased safety because there is better, more accurate categorization of the donor as to their eligibility.

[Slide.]

Here is an example of what it might look like. The very visit current questions that have to be asked, and to get these, I literally did a cut and paste of the current Red Cross questionnaire, and just thought in terms of these broad categories, are very limited in number.

Are you in good health? Do you have an infection? Are you pregnant? Have you been pregnant

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recently? Those are really the only things that have to be updated each time.

[Slide.]

Then, the questions that I would say, even though they are time-limited, should be asked specifically each time, are those related primarily to hepatitis exposure and HIV exposure. Have you been in close contact with someone with hepatitis, the tattoo, ear piercing, needle to take illegal drugs, and CJD, which again is a moving variable in terms of the time line.

[Slide.]

Then, I told you I would introduce this concept of a capture question, and the proposal would be the following: that for all the other issues, we would ask three very simple questions, and it would be based on these concepts, that you know the history was okay up until the last donation, which was like 12 months ago, so the chances of you hearing anything that is going to be cause for deferral is very low.

So, you would group the related questions under a very simple, direct yes/no question that would be

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easily understood and hopefully get very reproducible results.

You would design that question in such a way that the majority of your repeat donors would say no, no, and no. What is an example of how that might be? Well, if you wanted to get at what is happening with their current health, you might not want to ask have you seen a doctor in the last year. That might be too big a net, because lots of people see doctors for routine care, and there are no significant findings. They are going for an annual checkup, they are going to have their blood pressure checked or their cholesterol monitored.

But maybe a little more focused question that still would be an okay response from the majority of donors, might be have you had any new diagnoses. The idea here is that you could clear maybe 70 percent of your repeat donors based on these capture questions, and then only if you get yes response do you delve into the related detailed questions that fall underneath that category.

I think an important--this is one of those things that I would watch out for if I were implementing

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this--benefit might be that when you have asked a capture question, it is very straightforward and it is very innocuous. Sure, I have had some health problems. Having said yes commits the donor to a conversation about why they said yes.

I think what that may do is close the door for some of the comfortable rationalizations that donors will occasionally apply to a donor eligibility question. They have said their health issues, now we are going to have to talk about it. They are committed already to the conversation. So, you have removed the opportunity for them to say, well, I think it was probably 1976 that I last did that, so I am sure I am okay.

What would they have to be?

[Slide.]

For the Red Cross questionnaire, there would only have to be three - Have you had a new sexual partner? Have you traveled or lived outside the United States except for Canada, Australia, New Zealand, or Japan? Have you had any new medical problems, diagnoses or treatments including vaccination?

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If the answer to all of those is no, then, there is nothing else that you care about for the donor that you need to specifically query. If they answer yes, then, you delve into the detail. Let me show you what detail would be under, for example, Have you had a new sexual partner.

It would be all the questions related to the nature of that encounter and the sexual partner's risk behavior. Did you have sex with someone who had ever used a needle for illegal or nonprescription drugs? Did you have sex with another male? Did you take money or drugs for sex or have sex with someone who had taken money or drugs? Did you have sex with anyone who had taken clotting factors, anyone who has AIDS or tested positive? Did you have sex with anyone who was born in or lived in Africa?

Then, you would go to yet another tier if the answer to that subquestion now is yes. Then, the questioning would involve the HIV Group O category, so if it was someone who was in Africa, then, was it Cameroon, Central African Republic, Chad, et cetera. So, only after in some cases three layers of questioning would you

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be down to the level of detail that we currently try to capture in the first question that is presented to the donor.

[Slide.]

An abbreviated questionnaire has potential to increase the accuracy of the health history, which is actually a blood safety improvement potential. It has the added benefit, although it wouldn't be the only reason obviously to implement it, of improving donor satisfaction and decreasing costs.

I think anything that is done, though, with an abbreviated questionnaire sits in this much bigger context that we have been talking about so far today, which is are the questions, as they are asked, understandable, do they elicit the histories that put a fishing line into the donor that you want to follow through to see if it's a cod or a halibut.

You know, you want a way to capture all those donors who are at increased risk, so that you can funnel down to the actual behavior or feature of their health history that identifies them at higher risk, and those verifications that, in fact, your capture questions, your

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discrimination questions, however you build the hierarchy does that effectively is generic for an abbreviated questionnaire or a complete questionnaire.

I would suggest, though, that if we were going to move with something like this, a couple of sort of baseline things would have to be identified. One would be a parameter--and I hope we talk more about this at the end of today--a parameter that we would accept as reflecting a donor health history process that is at least equivalent to what we do currently.

It is unlikely that that parameter can be some kind of a humongous study of infection rates in transfusion recipients. It might not even be possible for that to be information about seroconversion rates with one questionnaire versus another in the clear donor population, but perhaps, especially given the REDS study data, which consistently shows this correlation between prevalence and incidence in donors, perhaps since it is the incidence we care about, we could agree to something like prevalence, marker rate prevalence as being a parameter that could be used to show equivalence in terms

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of the populations that are cleared by various donor health history instruments.

It would also require that the expectations for donor eligibility be stated in terms of the intent, not in terms of the actual question, because if the regulation is to specify a particular question or set of questions that are verbatim to appear on the questionnaire, then, you lose the opportunity for things like layered questioning with a capture question and then a series of focused questions.

But insofar as those criteria are defined generically, without a specific question being identified, then, I think there is a lot of opportunity for perhaps more clever, certainly quicker and maybe even potentially better, more accurate ways of eliciting the history that will allow the correct donor eligibility assessment at the end.

That's it.

[Applause.]

DR. LEE: Thank you, Dr. Chambers.

Now, we shall hear from the FDA side of things in terms of viewpoints on abbreviated questionnaire. To

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handle this difficult task, I have been successful in recruiting Ms. Elizabeth Callaghan. She is an interdisciplinary scientist in the Office of Blood Research and Review, CBER, and she works in the immediate office of the director and is responsible for the Blood Action Plan and the rewrite of the requirements in the Code of Federal Regulations.

Ms. Callaghan on FDA's Position on Abbreviated Questionnaires.

FDA's Position on Abbreviated Questionnaires

MS. CALLAGHAN: The topic of my talk today is FDA's Position on the Abbreviated Questionnaire. I apologize that some of the information in my talk has been presented previously today, but you can just all think of yourself as repeat donors listening to the medical history questions again.

I plan to give you a little bit of the background leading up to FDA's recommendation for using abbreviated donor screening material, and then present some of the concerns using the abbreviated material brings to light.

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With the onset of the AIDS epidemic in the 1980s, and in the absence of an identified causative agent, both FDA and industry instituted procedures to help prevent possibly infected individuals from donating blood and blood components and possibly infected units from either being transfused to patients or further manufactured into blood derivatives.

[Slide.]

One of the first memoranda concerning AIDS to be issued by the FDA was on March 24, 1983. This memo recommended that blood banking establishments that collect blood for transfusion institute the following steps - provide educational material to prospective donors, advising them to refrain from donating if they belong to a group that was at increased risk for AIDS, to re-educate donor screening personnel to recognize early signs and symptoms of AIDS, and to ask specific questions designed to detect possible AIDS symptoms or exposure, and to rewrite SOP's to include appropriate handling and labeling of potentially infected units.

Clearly, the first two items measurably increase the time required to perform the donor screening process.

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By the following year, the etiologic agent that caused AIDS had been identified. Of course, we all know it was called HTLV-3 then.

[Slide.]

On December 14th, 1984, FDA issued another memorandum which broadened the scope of the previous one. It was recommended that establishments that collect source plasma for further manufacture also include the previous mentioned procedures at their facilities.

In addition, the memo recommended that all blood establishments that collect blood for transfusion institute measures to increase the effectiveness of the voluntary self-exclusion procedures, hence, the birth of the confidential unit exclusion of CUE, the use of which was usually explained during the time the donor was going through the screening process.

[Slide.]

Over the years, additional memoranda were issued which recommended additional questions to ask donors during the screening process to further reduce the number of blood and blood components collected from donors at increased risk of AIDS.

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The memos also recommended that the AIDS information be presented to donors in both written and oral form. However, in addition to the AIDS educational information and AIDS questions, other questions were being added to the donor screening process.

[Slide.]

These included such things as inquiring if the donor had taken Accutane or if the donor had received human pituitary-derived growth hormone. Along with the FDA recommendations, whole blood and source plasma organizations were developing their own set of questions, which were being added to the donor screening process.

[Slide.]

Obviously, these additional questions and recommendations increased the amount of time it would take to perform an individual donor screening. For repeat donors, it had become a lengthy and redundant procedure. With millions of units of blood and blood components including source plasma being collected each year, it equated to a great deal of time and money being spent on the donor screening process.

[Slide.]

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Enter CBER to save the day.

[Slide.]

In February of 1990, FDA issued another memo to all registered blood establishments, which replaced the previous AIDS memorandum. Although the basic recommendations for the donor screening criteria remain the same as in the previous memos, one very interesting phrase was added. This was, "In some settings it is appropriate to use abbreviated materials for frequent repeat donors, such as serial source plasma donors, who may be screened as often as twice in a seven-day period, and who are familiar with the program employed in the establishment."

[Slide.]

This language was further modified in the December 5th, 1990 memo to include a recommendation to allow abbreviated materials to be used for autologous donors.

[Slide.]

Many source plasma establishments and blood banking establishments that collected units for autologous transfusion developed procedure for using

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abbreviated screening material and submitted them to CBER for review and approval. These procedures have now been in use for approximately a decade.

[Slide.]

All this said, it is important to remember that a donor screening is the first layer of safety in preventing inappropriate units of blood and blood components from entering the blood supply, so there is always concern about the effectiveness and thoroughness of the screening procedure.

This concern is even higher when the use of an abbreviated donor screening material is instituted. In today's collection facilities with the donor screening process getting longer and longer, the desire to extend the use of abbreviated screening material to additional repeat donors is the subject of much discussion, however if blood collection establishments plan to consider extending the use of abbreviated screening material to additional donors, or further modifying the abbreviated screening process that now exists, many questions should be considered besides that the questionnaire capture all the essential information.

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[Slide.]

Some of these questions are: What should the definition of a repeat donor be - twice a year, twice a week, or some other time frame? Should the long questionnaire be used periodically or if the donor does not donate for a long period of time, and if so, what should that time frame be?

[Slide.]

If the donor is processed using the long questionnaire and that donor neglected to provide some of the information, would obtaining that information be lost until the next long questionnaire cycle if the establishment is using an abbreviated format?

[Slide.]

If the donor presents new information during the abbreviated screening process, which is not necessarily included in the shortened procedure, how will the information be acted on?

[Slide.]

Should the abbreviated questionnaire be just a consolidation of the many questions of the long questionnaire? If so, what procedures should you have in

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place if a donor answers in a negative way to one of the multi-part questions?

[Slide.]

If the long questionnaire is revised, should it be administered to the repeat donor at the next donation even if it is not in the time frame for that donor to be processed with the long questionnaire?

How will establishments ensure that the donors are being processed with the appropriate questionnaire?

Things to consider.

[Applause.]

DR. LEE: Thank you, Liz.

I am afraid we heard a bunch of questions and no answers, but we will settle all the answers during the panel discussion.

We have a break coming up. The time now is 2:40 and I think we can break for 15 minutes, and we will reconvene promptly at five until 3:00.

[Recess.]

DR. LEE: We have heard quite a bit about validation issues. We have heard about how it is related to abbreviated questionnaire from both the industry and

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the FDA, and now we will continue our discussion on the topic of Local versus Universal Questionnaires, yet again another twist to the complexity of validating the donor history questionnaire.

For the next speaker, we have the pleasure of hearing from Dr. Merlyn Sayers, who has been with the Carter Bloodcare Center and also with the University of Texas Medical School, and he will talk to us about the AABB viewpoints on the national versus local donor history questionnaire, to be followed by Dr. Kurt Kroemer on the same subject.

Dr. Sayers.

NATIONAL VS. LOCAL DONOR QUESTIONNAIRES

AABB Viewpoints

DR. SAYERS: Thanks, Dr. Lee.

[Slide.]

I am actually going to have to start out with a disclaimer. I am saying some AABB viewpoints here, but I really don't want anything that I have to say to be construed as AABB official position. These are more comments and a few thoughts on some of these issues that have to do with streamlining the donor questionnaire, and

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if any of you came here suspecting that you were not going to hear much on the national versus local issue, let me assure you that your suspicions are well founded, for that is a very, very tough issue.

What I would say, though, is that my comments really are going to have to do with a sense of gratitude with the FDA's sense that there does have to be some streamlining in the donor questionnaire. At the hurley-burley end of our activity, drawing donors, recruiting donors, and what have you, the increasing sense of frustration on their part, going through the same ritualized process time and time again really does create in them a sense of dismay, disinterest on some occasions, and also because of the length of the donor registration process and the donor history, we are falling increasingly afoul of some of those larger corporations that enable us to draw blood donors at their sites because we are just taking so much longer keeping their staff off the production lines and certainly earning the disfavor of organizations which up to very recently had been powerful supporters of community blood programs.

[Slide.]

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So, let's consider some questions. Should local vernacular and idiom be recognized in the wording used in the donor interrogation, and this is probably a redundant question. Well, I could have said inquisition, but we will leave it at interrogation.

It is probably a redundant question because those individuals, the medical historians are going to have to correct the misunderstanding of those donors that do pose questions in response to what they are being asked, and those medical historians are obviously going to be conversing with the donor and responding to his or her queries in the language and the parlance which is local and which is most comfortable for the two.

Now, at what point does complexity in the donor questions defeat the purpose of the interview? You know, the interview has become as much a challenge for the medical historian as it is a challenge for the donor.

It used to be that the medical historian except in California was an individual who was an entry level person, but nowadays those entry level individuals are youngsters that we now require to confront, face to face, donors who might be old enough to be their parents, and

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we require those medical historians to have a knowledge of sexually transmitted diseases, parasitology, geography, infectious disease, medicine, surgery, a whole host of disciplines.

We require in them a smattering of knowledge, so that in response to donors' queries, they can present themselves authoritatively and inspire the sort of confidence that we want our staff to create in the donor during the donor process.

What about this question, "Are there risks to increasing the number of questions that donors are asked?"

I would have to refer you back to a study which was done by Mayo and others from the American Institute of Research some 10 years ago, and they were looking at new ways to question blood donors.

One of the remarks that that group made in their paper en passant was the fact that 52 percent of donors were seen to ignore some of the material that was presented to them, even though that self-same group of donors did allege emphatically that they did not ignore anything, but they were actually witnessed to having

ignored some of the material that was being given to them.

[Slide.]

What about a caution before we assume that questionnaires serve their purpose? I sometimes think that what we are really trying to do is make a silk purse out of a sow's ear. We have got this questionnaire, and what we have heard of today, there is a lot of the restrictions to its efficient and accurate implementation.

Here is another restriction. In 1992, the National Adult Literacy Survey--and you can look at it off this side if you are so inclined--40 to 44 million of the 191 million adults in this country demonstrated skills in the lowest level of prose, document, and quantitative proficiencies. Being translated, 40 to 44 million individuals cannot accurately and consistently and with confidence translate the instructions on their prescription medicine containers.

What was particular damning was this observation. The literacy proficiencies of young adults was somewhat lower on average than the proficiencies of

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young adults who participated in a 1985 survey. Sad news.

Let me say emphatically that this really is not an appeal for scrutiny by intelligence quotient, by donor aptitude tests, by comprehension testing, by some sort of donor entrance exam, making this observation is not an appeal for an additional layer of scrutiny as much as it is an appeal for ensuring that we do pitch the questions at a level which we suspect is going to be intelligible to the majority.

Well, let me make a few comments about a role for vernacular and idiom. I just picked out a couple which have been brought to my attention in our experience in Texas. What could be simpler than the question, "Are you under a doctor's care?"

Now, some donors who might be seeing their physicians regularly for checkups for their diabetes or for some other disease do not regard anything other than an emergency visit to a physician as being under a doctor's care.

I was interested to hear that the question could also be worded, "Are you doctoring?" Some good folk

would understand are you doctoring, whereas, they might not understand are you under a doctor's care.

Where the question are you doctoring is problematic is it becomes confused with, "In the past 12 months have you taken cocaine through your nose," because one of the innumerable euphemisms for cocaine is doctor snow, and in some parts, "Are you doctoring" is a roundabout way of asking are you inhaling cocaine.

What about, "In the past 12 months, have you had a positive test for syphilis?" Well, I can't begin to tell you how many alternative ways there are referring to that disease. I mean historically, there were these wonderful international insults. The English refer to it as the French disease, the French refer to it as the English disease.

Locally, at least in our experience, the majority of individuals who would ask specifically for more details about this question regard any encounter at a sexually transmitted disease clinic as being a treatment for syphilis. They do not discriminate between the various entities for which they could be treated at those destinations.

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What about, "In the past 12 months, have you been in jail?" Well, have you been in the pen, have you been in the poky, have you been in detention, have you been in juvenile hall, have you been in holding, have you done time? The possibilities go on and on and on.

There has to be some role for vernacular, and there has to be some general level of understanding of questions which superficially look as if they are eminently understandable to all of us, but in the local context, may well take on a slightly different shade of meaning.

[Slide.]

We have already heard from Dr. Boyle that even in this nation's highest elected office, there is discomfort with understanding what "having sex with" actually means, and the choice of alternative wording I have got here ranges from the genteel slept with, been intimate with, have intercourse with, had knowledge of, in one wants to be biblical, to the obscene, and this is a wonderful reference, The Dictionary of the Vulgar Tongue, and I would refer you to that if you want to look

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towards the more scatological ways that that question can be phrased.

I think there should be an emphasis on how questions are phrased, and there should be an opportunity to pitch them in what might be a local context, but it has to be with the understanding that there has to be absolute clarity on the part of the blood program in knowing what they want the donor to appreciate by the question.

[Slide.]

I said I was going to say something about complexity, and I have learned from Dr. Boyle this new phrase, "Time bound events." It really is, in our questionnaire, a matter of when, and I could show you this illustration, and it could be a test for blood bankers.

What are we referring to today, what are we referring to for two days, for four weeks, six weeks, eight weeks, 12 months, three years, I mean what are the issues that we are trying to come to grips with when we say to somebody, "In the past two days, have you taken aspirin," or "In the past eight weeks, have you given

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blood before," or "In the past 12 months, have you been in contact with somebody with hepatitis or had a needle stick."

It does become very complex with a blood donor who has to recall what events might have occurred during these very narrow time frames, and I think here we sow the seed for all that mischief that we reap when individuals go home, relate to their partners or their household family what they went through during that day, only to be reminded that, well, of course, three years ago you were outside the United States.

The more complex we make these questions, particularly the time-related ones, the greater the vulnerability on our part to uncovering something which the donor was not accurate about in his or her recall.

Dr. Boyle made mention of how consistent donors are, and I thought I would never, ever confess this publicly, but there has to be a journal for unpublished but interesting information.

Ten years ago I got interested in donor questionnaires, and I selected 100 blood donors who had in common the fact that they had donated five times

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during the previous year. In those 100 individuals, I took out five questions that had to be answered consistently each time.

The extent to which those regular donors answered those questions consistently was deplorable, absolutely deplorable. The reason I did not publish that was twofold. One, I wasn't convinced that the fact that the responses were poor and inconsistent contributed to any morbidity and mortality in transfusion recipients, and two, when I broke the code as to which individuals had responded inconsistently, one of the most egregious offenders was myself.

[Slide.]

We are talking about complexity. What if the draft guidance on donor deferral related to xenotransplants, and that came out in December 1999. That was draft guidance. What if that had been adopted? One of the three new proposed questions would have been worded as follows: Have you, your sexual partner, any member of your household or any other close contact ever received human body fluids, cells, tissues, or organs that came in contact outside the body with the cells,

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tissues, or organs of an animal? That is verbatim from that draft publication.

We showed this to a number of donors, a few of whom deferred themselves. Two of the individuals that deferred themselves were subsequently interrogated by yours truly, and the confessions that I eked from them had to do with the fact that both, confronted with a long question, felt exasperated, skimmed it through, went no further than have you ever received human body fluids, and both of these individuals had been breast fed, and both of these individuals earnestly and sincerely would have deferred themselves.

I am really, and I must say this with emphasis, not attempting to in any way discredit the donor history process, I am certainly emphatically not trying to do that, but we really do have to be cautious when it comes to understanding what we want from donors, and we have to be equally cautious in making sure that we don't ask these questions in such a way that we lose the donor's sense of concentration, the donor's sense of proportion.

What about if this question had got through? What if the recommendation had been adopted to change the

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permanent deferral period for men who have had sex with other men, even one time, since 1977, to five years following MSM activity?

So, the revised question could read, "In the past 12 months, have you had sex with a male who has had sex, even once, with another male, but was not himself a male who had had sex with another male during the last five years?"

This MSM activity question is a burning issue, it really is. It is something that we need to address. It may be an opportunity for relaxing the conservatism in some of the history questions of the donors, but it hospital to be done in such a fashion that we do not end up with an element of our donor history process which approaches the complexity of a question like that.

[Slide.]

So much for complexity. What about the increasing number of questions? We have heard from the other presenters that there are questions within questions. One question can have tumbling into its context a whole host of other issues that cause the donor to pause and contemplate.

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These questions are from the CFR, the FDA memos and guidelines, AABB standards, technical manuals, and when you added up all the questions in the process, there were just slightly more than 60 in 1988, and the number of questions cumulatively now is more than 140.

I think Dr. Bianco and others have emphasized that this is an essential part of the donor process, but we do not know the sensitivity, neither do we know the specificity of any of these questions.

[Slide.]

I have never, ever used a cartoon before. This is the first and may well be the last, but it is just a reminder that a few more questions really has been the order of the day over the last 10, 12 years. The increasing number of questions are an element of exasperation in part of the donor experience, but they are also important to ensure that we contribute to decreasing morbidity and mortality from transfusion.

[Slide.]

There is a risk though. Here is the risk. Bear with me while I go through this slide. These are contours of constant probability of inappropriate

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deferral, and by "inappropriate deferral," I mean false positivity, the probability of false positivity.

We have got specificity of a screening procedure on this axis, running from about 97.9 percent to 95 percent, and we have got the number of lifetime donations per donor on that side, and what we are looking at is the likelihood that that individual is going to be deferred because of nonspecificity because of false positivity in a screening test.

Not, intuitively, the more often an individual donates, the greater the likelihood that he or she is going to fall afoul of this process and earn a false positive result.

There is a 50 percent chance that if the screening test has a 97 or 98 percent specificity, a 50 percent chance of that individual is going to be deferred after some 30 donations. As the specificity decays down to, say, 95 percent, that individual's 50 percent chance of being deferred for false positivity occurs much quicker, after only a dozen or so donations.

We have been used to thinking about these relationships in terms of serological tests, but we have

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got 150 donor questions to add to this process, each one of which has an unknown sensitivity and specificity. We do not know, but we can suspect that these nonspecificities are cumulative. What do we achieve at that point?

Let's say we have a specificity which goes from 90 percent, now down to 50 percent for the overall process which includes all the serological testing and all the history questions.

An individual has now, at 90 percent specificity, cumulative specificity for the process, got a 90 percent chance of deferral after 20 donations. If that specificity gets down to 50 percent, that individual has a 90 percent chance of being deferred after a scant four donations.

What we are creating with all this increasing testing and increasing interrogation is a system which is hostile to the very individuals that we want to retain in the system, the repeat volunteer donor.

So, we do need the serological testing obviously. We do need the donor history obviously. But we need to make sure that we do not in demonstrating our

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industry and purpose in making sure that the interrogation and the serological testing is as extensive as it should be, we have to make sure that we do not run afoul of this set of circumstances and create a huge cadre of individuals who are deferred for no reason greater than nonspecificity.

I don't want this to sound like a sermon, so I am going to leave you just with this quotation. It is out of the 8th edition of Standards, but I could have taken it out of the 1977 Standards, because that is I think when it first appeared.

"We are going to have to ask some very specific questions, but a great deal of pertinent information can be obtained by using some general or leading questions in simple language that the donor can understand."

Thanks.

[Applause.]

DR. LEE: Thank you, Dr. Sayers. That was a very enlightening talk.

As a Part 2 of the same topic, we will now hear from Mr. Kurt Kroemer, who is the Director of Regulatory

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Affairs in the Government Relations Department of the American Red Cross.

Mr. Kroemer.

MR. KROEMER: I was asked today to speak, not in my present role, but in my former role with the U.S. General Accounting Office where I headed a number of projects looking at all sorts of biological products, but in this particular case, I was looking at the safety of the blood supply.

[Slide.]

That report was completed in February 1997. I am sure most of you are aware of it, but I will just go through some real quick, sort of underline issues with that. The purpose was to determine what the elements of FDA's layers of safety were and whether they actually ensured the safety of the blood supply.

We looked at the five, so-called overlapping layers of safety, donor screening, deferral registries, testing, quarantining, and monitoring.

[Slide.]

We made a number of recommendations in that report. Here is five of the nine. Notifying deferred

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donors, viral testing of autologous units, confirmatory testing of repeat reactive units, lookback--and that was not universal lookback, that was only to 1990--and reporting of errors and accidents by unlicensed facilities.

[Slide.]

In our findings, we didn't make any specific recommendation on the donor history questionnaire, however, in what we call our "Results in Brief" section of the report, we noted that there was a lack of a uniform donor questionnaire, and that allowed for variability in donor screening.

Also, in the "Principal Findings" section, which delineated a number of areas within the five layers of safety for donor screening, we highlighted privacy concerns during history taking, and that we noted in some of our travels to different blood banks throughout the country.

[Slide.]

Specifically, with the donor questionnaire, when we went out to the site visits and when we looked at the different questionnaires, obviously, what we found was

that the types of questions asked and the manner in which they were asked differed from facility to facility, and even though you have this AABB uniform questionnaire, when we sat in on some of these donor history takings, that the donor actually allowed us to do that in the blood bank, that even when you had sort of the specific question there, within the AABB uniform questionnaire, that question was asked differently.

It wasn't a huge difference, but as we found out throughout the discussions today, subtle differences can sometimes have dramatic differences.

Also, the level of privacy within different blood banks was different. Some were very private, some we felt were completely not private. It is unclear to me whether that has changed a bit. This was obviously since 1997, and I think blood banks are working toward that, but I am not sure that even today I would consider that all of the privacy areas are, in fact, completely private.

We also went through literature review, and I am sure most of you are aware of a lot of these different heavily cited kinds of results, asking donors blunt and

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direct questions screen out more high risk donors than less direct questions, and donors do not appear to be offended by explicit questioning.

[Slide.]

Also, direct questioning probably results in deferral of at-risk but predominantly non-positive HIV donors. Even though this is citations from '91 and '94, I think that they are clearly still relevant today.

Understanding cultural influences are crucial in determining at-risk behaviors, and screening areas, in fact, as I just stated, provide inadequate privacy, and donors would give different answers had they been in a more private setting.

[Slide.]

One of the workshop objectives that I saw when I got some of the material was to analyze error and accident reports, and that is precisely what we did when we went through a number of these. We broke it down by facility type and we also did it by rate per facility and rate per 100,000 units collected. What we basically did was divide the number of facilities by those error and

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accident reports or by the total number of units collected.

We found differences, however, we weren't able to really come to any common conclusion on this because there were all sorts of intervening variables that could help explain whatever differences we found there, so I don't think anybody can really conclude anything specifically from that except to suggest obviously that there are these error and accidents occurring during donor screening.

[Slide.]

Then, we also went through a representative sample of establishment inspection reports. We went through about 401 inspection reports, and some of these are two pages long and some can be hundreds of pages long.

What we looked at was the donor screening problems that the FDA inspectors found. So, facilities with problems, those were actually when you went through the inspection report, you found something where an FDA inspector noted on the report, gee, there is this

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particular issue with the donor screening at this particular facility.

The second line, the facilities with Form 483 observations, was that the inspector found the problem problematic enough, egregious enough to cite that particular facility for a donor screening problem on the 483 item.

Again, there are differences, although if you look at the licensed versus the plasma centers, it is the same, and again it is hard to conclude what any of this specifically means because of the different things that are going on in the facilities, however, overall, again, there are clearly problems that were occurring at these facilities that FDA was finding.

[Slide.]

Lastly, AABB wanted me to discuss what was our thinking while we were going through the different findings that we found, and for the questionnaire, the style and content of history taking may influence the accuracy. The lack of a uniform questionnaire results in variability, and as opposed to "lack of," I probably

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should have put differences in donor privacy results in additional variability.

I remember sitting around a table with a number of us at GAO, and we were going through all of our findings and trying to determine what did we want to recommend, what did we just want to have as a finding, and we didn't feel as though these different variabilities were so problematic that they lent themselves to a recommendation. We thought that there were other things that were more problematic.

However, we did feel as though we needed to point them out in the different results in brief and finding sections, and the end result, I think what we were thinking about that table was that decreasing variability is a good thing, and that we can talk about different vernacular and we can talk about--I mean people in the past anyway have talked about perhaps different sections of the country might have a question about Chagas' disease, and maybe others wouldn't, and as we well know, that may be problematic now.

So, in the end analysis, what we wanted to conclude with that was that whatever could be done so

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that donors are being asked the same questions, and that you are not bringing in intervening types of variables, intervening questions that then you are not really getting to the same kinds of responses across the country, and therefore, you are in fact increasing that variability, that we felt that that needed to be minimized.

That's it. Thank you.

[Applause.]

DR. LEE: Thank you, Mr. Kroemer.

Now, for our last presentation of the day, we have the pleasure of hearing from Dr. Elliot Cowan. Dr. Cowan is currently serving as the Chief of the HTLV Section in the Division of Emerging and Transfusion Transmitted Diseases, Office of Blood Research and Review, and he is responsible for all issues related to HTLV and blood safety as CBER including the licensing of blood donor screening tests for HTLV. Dr. Cowan tackles this topic with some trepidation, but with much success.

Dr. Cowan.

FDA Viewpoints

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DR. COWAN: How do I talk after a lead-in like that? I will try as hard as I can for those of you who know me and there may even be some of you out there who do, not to talk about HTLV. I may slip, so just pardon that.

One other thing I wanted to mention, the slides that I have are slightly different than the ones that you have in your handout. Joe Wilczek said that he would post the version I am about to show you on the web site, so I apologize for any differences between what you have actually in your handout and what you will see up here. There are some minor differences.

[Slide.]

I am indeed going to try, and I underline the word "try," to tackle this issue of national versus local donor questionnaires, and I am not sure how far I am really going to get with it other than to I hope raise a few issues. I don't think I am going to be able to answer any questions--I know I am not going to be able to answer any questions, but these are some of the questions that I am going to try to address.

[Slide.]

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First, where are we now? Second, what exactly is the difference between a national and a local questionnaire in the context of the blood supply? How can changes be made and what types of changes are being proposed? This is where I kind of lapse into the old FDA regulatory mode, so please bear with me on this.

Are the changes effective in achieving the desired result? That gets back to some of the things you have today. Actually, a lot of what I am going to talk about gets back to what you have heard earlier today.

[Slide.]

Where are we now? We have essentially a "one size fits all" donor questionnaire, which is perceived as cumbersome and burdensome, which is precisely why we are here today, burdensome because there is the perceived redundancy of some of the questions, some embarrassing private questions, too many questions that take too much time, and questions that don't seem relevant to all blood donors that walk through the door.

Some questions are not relevant in certain geographic areas. For example, areas that are non-

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endemic for a particular etiologic agent. I am going to touch on that a fair amount in just a little bit.

[Slide.]

What are "national" and "local" in the context of the blood supply? National donor questionnaire is uniform across all blood centers across the county. On the other hand, a local donor questionnaire involves variations on the uniform questionnaire from one blood center to another. That is one type of a local question.

Another is something altogether different, which is what we call a "from scratch" questionnaire used in-house by a specific blood center.

[Slide.]

Let me go through now some pros and cons for the national and the local donor questionnaires. First of all, one of the advantages of a national questionnaire is it is uniform and standard, and it provides harmonization. On the other hand, one size really doesn't fit all, all donors across the country in different areas are really not the same.

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Second, an advantage is there is no need for repeat validation, on the other hand, validation for one donor group may not be applicable to others.

Another advantage of the national questionnaire is that repeat donors know exactly what to expect, and this was talked about a few times today, that familiarity expedites the donor interview.

[Slide.]

In terms of the local questionnaire, an advantage is that it accounts for local donor differences, but on the other hand, it is not known if donor profiles really do differ locally, because donors do travel.

Secondly, an advantage is there is the opportunity for streamlining, on the other hand, there is an increased chance for confusion. There is no validation or standardization involved.

Another potential advantage for the local questionnaire is there is the opportunity to generate information about local donor differences, and we can move on from that.

[Slide.]

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Some of the reasons why we would have local questionnaires--and this is something that the last two speakers spoke about--and that is the wording. To accommodate local social issues, idioms, linguistic issues, the wording of questions that may vary from region to region. Something I wanted to mention, by the way, the two comments that Dr. Sayers shared with you about MSM and about xenotransplants, I didn't write it. Set the record straight.

Another reason for local donor questionnaires is that questions that would address immediate health concerns, such as sudden appearance of a new infectious agent or an outbreak. Finally, there are questions that could address local health concerns that are based on epidemiology.

[Slide.]

In terms of immediate health concerns, again, the sudden appearance of a new infectious agent, for example, troops returning from an endemic area outside of the U.S. to their base. Another example would be tick infestation which occurred at Fort Jaffe in Arkansas a

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couple of years ago, something that happened immediately and was of acute concern to the blood supply.

On the other hand, the local health concerns which are defined by epidemiology, and are a bit--I have to put it in quotes--"more stable." Some examples of these are some of the tickborne diseases, such as babesiosis, Lyme disease, and Rocky Mountain Spotted Fever, and also the Trypanosome disease or Chagas.

What I think we have to ask is what are the risks associated with these locality-based questions, what is the likelihood of an infected donor in a non-endemic area, and is this a realistic consideration. I just throw this out for your consideration. People do travel, and how local is local.

[Slide.]

Here is where I get into some of the FDA jargon, I guess. The next few slides are going to be based on a draft guidance which is out on the web site. The location of that is listed down here, and that is correct on your handout.

It is called the Draft Guidance for Industry: Changes to an Approved Application, Biological Products,

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Human Blood and Blood Components Intended for Transfusion or for Further Manufacture. I didn't write that either.

It actually is a very interesting document, and I emphasize it is in draft form and some of the references, I am going to show you the sections which are listed on your handouts, which are the same in your handouts as on the slide. They may change actually in the final version, which will eventually come out.

[Slide.]

What are the categories of changes? Well, first of all, there are changes that could be described in an annual report under Section 610.12. This is for licensed blood establishments, and this part in this section of the draft guidance that reads "Implementation of an FDA-approved AABB Uniform Donor History Questionnaire, if used without modifications or if modifications are more restrictive."

In other words, it is not viewed as a problem if a given blood center wants to make its questionnaire more restrictive than it actually is. If anything, that is more conservative.

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Of course, this doesn't apply, an annual report wouldn't apply to unlicensed blood establishments, wouldn't have to report that, but an unlicensed establishment would have to follow GMP's and the evaluation of compliance would be made during an FDA inspection.

[Slide.]

The second category is a major change, which would require a supplement under 610.12, again for licensed blood establishments. Donor history forms that deviate from the FDA-approved uniform donor history questionnaire.

An addition or revision of SOP for the following categories if the change is less restrictive as opposed to more restrictive than previously approved or is not addressed in published FDA guidance documents, and donor history forms are included here. Again, unlicensed blood establishments would be checked on during the inspection process.

[Slide.]

What types of changes are being proposed? If one would transition from a universal questionnaire or a

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national questionnaire to a local version. I think the most likely situation is that a core set of questions would actually be retained, which would be common to all blood centers.

What would happen then is either more questions would be added depending on the geographical area to address local concerns, and this would be more restrictive, and so would require just to mention in the annual report.

On the other hand, there may be a decision to delete some questions depending upon the geographical area. In this case, it would be less restrictive and would require a major supplement to be filed.

Another change that could take place, something we have talked about, of course, is a change in the wording, and this presents a very tricky issue because that really could be a minor change or it could be a major change. I think we would have to discuss that to see what sort of a submission, if any, would be required for wording. Sometimes it would be perceived as a very small change, and sometimes it could be more of a major change.

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[Slide.]

I would like to address the concept of validation, which Alan Williams talked about very nicely earlier, as well as I think a few other people, but I will just take a minute to go through this.

Also, from the draft guidance, "Before distributing a licensed product manufactured using a change, applicants are required to demonstrate, through appropriate validation and/or clinical or non-clinical laboratory studies, the lack of adverse effect of the change on the safety or effectiveness of the product." Of course, the key is how do you do the validation, and that is the trickiest part of this.

[Slide.]

This is really just a rehash of some of what Dr. Williams had said. For validation, determine if the revised question or questionnaire achieves its intended purpose. What is the positive predictive value, and, of course, the negative predictive value of the revised question or questionnaire. Why include or delete a question? What is the impact of the question or questionnaire on donations? How many more donors are

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deferred, how many unsuitable donors are accepted? Finally, the impact of the question on the donor in terms of comprehension. These are all things that we have covered already.

Just the last few slides to go over some of our viewpoints, I guess.

[Slide.]

First of all, the FDA views there to be a need to be proactive to prevent a new infection, in other words, not wait for an infection to occur is the stimulus for action.

Secondly, exercise caution when considering disease localization. I had actually planned on showing a map of the United States and how the tickborne diseases are suddenly appearing everywhere, when it seemed like they are located in one particular area or another.

It is difficult to localize. The question I think we have to address here with formal scientific studies is, is it possible to build an epidemiological fence, is it difficult to conceive of long-term localization. We also have to consider the fact that we

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are a very mobile society. People travel, they resettle, and that presents all sorts of issues to us.

[Slide.]

Of course, validate that changes made are effective at identifying infected donors, and this gets to sensitivity and specificity, which Dr. Williams had brought up also, and I deal mostly with test kits, and we are really dealing with the same sorts of issues here. We have to think about the sensitivity and specificity issues in dealing with these questions, just as we would with a test kit.

[Slide.]

Also, ensure that changes don't impact negatively on the remainder of the questionnaire. If you change one thing, how much of an impact is going to have on the rest of the questionnaire. Each question doesn't necessarily stand by itself.

[Slide.]

Finally, the end and the means. The end is to specifically identify blood donors who potentially harbor transfusion-transmissible infectious agents to identify donors who would not be detected by current donor

screening technology, window period donors, or to circumvent the need to do costly testing especially supplemental testing, confirmatory testing.

The means, of course, is a well-constructed, effective donor questionnaire, and I, for one, am actually quite encouraged with all of the ideas that have been bounced around today. I would only hope that some action can be taken on those to achieve the end of having a more streamlined questionnaire.

Thank you.

[Applause.]

DR. LEE: Thank you, Dr. Cowan. I am glad that you didn't bring up more questions than has already been raised here.

It has been a long day. We heard a lot of interesting presentations. At this point I would like to just take a minute to thank all the presenters for the wonderful information they have provided us, and also for staying on time. Thank you all.

[Applause.]

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DR. LEE: I would also extend my thanks to Mr. Joe Wilczek here, who is behind the scenes making everything happen. Thank you, Joe.

[Applause.]

DR. LEE: Also, the remaining members of the workshop organizing committee. I think some of them are in the audience. Thank you.

At this point I would like to call every presenter that is still here, not just from the previous session, but from the entire day, to come down to the panel and we will begin perhaps the most critical portion of this workshop in bouncing off ideas from one another.

Panel Discussion

DR. LEE: This is not necessarily a panel to answer questions from the rest of the workshop participants, but really a session to expedite discussion among everyone, so please feel free to cross-examine each other and try to generate as much information as we can. We have already heard a lot of wonderful information, I am sure more will follow in the ensuing discussion.

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Are there any burning questions that anyone would like to start off with? The panel member takes priority.

MS. O'CALLAGHAN: For Dr. Chambers. You had indicated that the Red Cross had identified post-donation information reports, the cause for those to be that the donors didn't understand.

Do you have or anybody else have any real data to support that the reasons the donors don't give the information at the earlier donation is really because they didn't understand the questions or is there other underlying reason for not having that?

DR. CHAMBERS: That is entirely from anecdote. I know that it occurs. What percent of the post-donation information is in that category, I couldn't tell you, but I would love to find out.

I would love to take post-donation information and subgroup it into real callbacks where a donor says, you know, I got home and I was talking to my mother, and she said you had hepatitis when you were 18, remember when we were at Uncle Joe's, versus somebody who comes back for a subsequent donation, gives the same history

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that is assessed for the first time correctly in terms of ineligibility.

Those are like subsequent donation information encounters. In one case it is no fault of the questionnaire necessarily, it is just the donor's recollection, and the way you fix that maybe is to get information out ahead of time, so people are thinking and soliciting their health history before they ever appear to donate.

When the issue is that they have come for a subsequent donation and given the same history, and had a different assessment, that can be a health historian failure, it can be a failure of documentation, it can be a training issue, it could also be a communication issue.

Both things could occur if the question is bad, as well. So, I think a real careful look at post-donation information cases, for whatever wisdom you can milk out of it, about how donors respond to the questions, how good the questions are, and how good the health historians are at applying them would be worth the effort.

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It occurs to me that post-donation information is like a natural--what is the word I am looking for--it's an audit in a sense of a process, and it's an error that could be I think teased apart right back to try to assess what the core problem was.

It is another way of saying the same thing, I think it is very fertile ground for learning more about how our questions perform, how our donors understand them, and how our health historians work with the donors to properly or improperly tease out the final decision about their eligibility status.

There is anecdotes for all of those things that I described as occurring. I don't have any perspective, but I think I am going to try to get it, in fact, let's swap cards because you have got the bigger database. I mean I have half of the action accessible to me, but you have got the rest of it.

Now, it would take some work. You would have to, in some cases, get ahold of the donors and get more information in order to really determine whether that first encounter with an assessment that they were okay, that was then not okay on the subsequent visit, was

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really what the donor reported or whether they reported everything and it was misassessed by the health historian.

So, it would take maybe some background work in order to get things properly categorized, but it could be very illuminating.

MS. O'CALLAGHAN: To follow up with that, with the number of post-donation reports that we have, by abbreviating the donor history questionnaire, I am real concerned that if you ask, you know, what has been said a couple of times by several people today, is that you ask these real direct questions the first time this donor comes in, and you assess them and you make sure that they are giving you all the right information, and then you only ask them partial questions at the subsequent donations, are you missing the opportunity to get that post-donation information by not asking the same questions, because these donors are not answering the questions the same way, being asked these real specific questions every time.

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So, I think trying to understand why they are not asking these would also give some insight to whether or not you are going to be missing good information.

DR. CHAMBERS: I agree with you, and I would say if you were going to try to develop an abbreviated donor history questionnaire program, you would want that perspective in order to know at the beginning how many times you ask the complete questionnaire before you are assured that you have obtained all the historical information, and it is documented, assessed, and found to be okay.

You would only be guessing if you picked a number right now because you don't know unless again you pick apart those post-donation information cases and see whether you ever really do get relevant information that is cause for deferral that is correct.

Again, you have got to get back to the donor and really wrestle with whether this information was shared in the same way with the previous donations and misassessed or whether it is really new information, but having done that, to see how often you really get new information on the fifth or sixth or seventh encounter,

or how often as we suspect they cluster around that second and third donation period.

I don't think anybody knows.

DR. LEE: Dr. Williams.

DR. WILLIAMS: I will change the subject a little bit and take it back to the final discussion topic, that of local versus national questionnaire.

One of the elements that wasn't discussed is that although syphilis can be described with different terminology and infectious diseases can be focused, there is also the issue of differential interpretation of the science that is available in terms of providing a safe blood supply.

Whether existing literature supports implementing a question, the opinions may vary between blood centers, and I would refer you specifically to the intranasal cocaine question. So, perhaps the question is should there be ability to introduce a question at a single blood center or a group of blood centers which, by standard of care or other mechanism, becomes a standard for the country, or should this be a regulated activity

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which is done by a centralized decision process to assess the science on a standardized basis.

I think it is a little more provocative and a little more complex question, but I think that it is real world situation.

DR. LEE: Dr. Bianco.

DR. BIANCO: If the question is being provocative here, as we think about the question that Sharon was asking of Linda, or the issues that you raised, I see that we have a couple of immense obstacles that we have to overcome in order to streamline blood donor history.

I think that the first one is that we work on the basis of an assumption that I don't know how to get rid of it, that the current medical history is validated and it's good, and that if we change anything, we run the risk of making it worse.

I am not sure that that is true, I am not sure on how we can deal with it, but that is I think my major concern, that is exactly, Sharon, the type of questions that you asked, what if the donors then modify. It would

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be true if the current questions were perfect, and I think that we heard today that they are not.

The other concern is we are asking question by question, and it's because I think of myself, I am unable to deal with a problem that is bigger than this, but we are asking the question, is the entire process of the many questions that we have. If the outcome is the outcome that we want, and if we tweak a little bit here, we add a question, we take a question, and all that, what is the overall outcome, how do we validate this outcome.

I think that the outcome is in a certain way--I don't know if by the questions--but we have the outcome of the system, and we know that the system today produces a degree of safety, safer than it was, let's say, 15 years ago or 20 years ago when we were dealing with those issues.

So, I think that we will have to be a little bit more courageous and maybe take some steps to simplify some of those questions, and maybe it may appear like some risk for those that are very concerned with change, but I think that unless we have the courage, we are not going to be able to improve the process.

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DR. LEE: Dr. Fridey.

DR. FRIDEY: There is also one very fundamental issue that I think really hasn't been addressed today, and we had requested that someone from the FDA address that, and it is to give us a definition of streamlining. I am wondering if there is anybody here from the FDA who could provide that for us.

DR. LEE: In Dr. Epstein's opening remarks, he did not necessarily call it a definition for streamlining, but he had a slide in which it indicated goals and then issues to consider. I think he stated that the goals of streamlining the donor selection process, and he termed it more broadly than the questionnaire, he actually called it a donor selection process.

I think his intention was to include the computer-assisted interview and the entire process of selecting the right donor before you proceed to phlebotomy. In his "definition" of the streamlining the donor selection process, the goal that he identified was that it is to modify the existing donor selection

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process, I think, such that we strike a right balance and optimize among three key factors.

I think the ones he identified were donor protection, blood safety or recipient protection, and lastly blood availability, and the burdensomeness and the unnecessary donor deferrals that we have been talking about all day long really speaks to the blood availability issue.

So, I think the goals that he stated in that statement can more or less serve as a definition, if you were to simply substitute the term "definition" there rather than "goal," I think we would be reasonably satisfied that is a working definition.

Of course, he expanded on that with seven or eight bullet points as to what he means, what factors should be considered in modifying the current selection process to a better one.

So, I don't think we necessarily called it a definition, but I think we had one. That is my recollection of this morning's talk from Dr. Epstein. Others may or may not add to that.

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Dr. Fridey, are you satisfied with that slide as a definition of streamlining?

DR. FRIDEY: I think some parameters were established. I am not sure that I can come away from this still understanding what the FDA means when it is talking about streamlining.

DR. LEE: I guess you are looking for some concrete recipe type instructions as to how we might streamline, and obviously, that is a very complex issue. Dr. Epstein's goals were directed more at conceptual goals rather than procedural ones.

So, I think the procedural ones are for all of us to fill in, fill in the cracks, so to speak, and that is in a way a charge to the committee right here sitting at this table, how should we modify to that end.

Dr. Boyle.

DR. BOYLE: Thank you. I would just like to make one observation from what I have seen today, and that is, my greatest concern after hearing a lot of good things today, is the committee that is charged with this responsibility having few resources to be able to do the

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type of scientific, comprehensive, systematic work necessary to address the needs here.

To put this in context, the VA recently signed a contract to do cognitive testing to make sure that their questionnaire for customer satisfaction with VA burial benefits was valid and useful. I would certainly hope the Public Health Service could find equal resources to address the issue of the uniform donor screening.

DR. LEE: Dr. Bianco.

DR. BIANCO: That is a good point, but I, since I am not part of the task force or the AABB committee, I feel very comfortable--

DR. LEE: Would you like to be a member?

DR. BIANCO: No, no. But I feel very comfortable pointing out something that I find interesting. I think that there is a tentative search on the committee and on FDA of what can the committee generate that would be acceptable to FDA. I think that that is how I heard the question from Joy. The goals that you related now and that Dr. Epstein related this morning, I think that all of us have that goal. We want

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it better. We want it better for ourselves, we want it better for the donors.

How can we achieve it and knowing that the FDA has a very strict set of rules and has a concern for their interpretation on protecting the public health, how much can we change within the system that would be acceptable to FDA. I think that that is a good reason for concern, and I think that the enthusiasm that the committee will have in terms of working very hard, digging for those resources that Dr. Boyle recognized that we don't have in order to do it, to come to an outcome that make all of us happy.

DR. LEE: Thank you. One thing that I have heard over and over today, but I haven't heard it phrased in such a way, is sort of an algorithmic approach to doing questioning. Many people have pointed out that once you ask a particular question, this was mostly in reference to the presentation by Dr. Sayers, that there may not be a need for other questions once you identify a big no up-front, a similar idea can apply to many other situations even the local versus national questionnaire issue, certainly for abbreviated or repeat donor.

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We have been adding items starting from many years ago until now, over 100 now, and it seems that one of the goals we might strive for is not necessarily to decrease the absolute number, but to devise a system where a particular donor is not exposed to all of them, that a particular donor is exposed to only a few major questions, and based on the response from that, then, you cycle to a particular deeper area of further questioning.

This is where the computer-assisted interview might come in as a useful tool, because it allows the donor to interact with the system in a say that tailors that system to that donor only.

This is a theme that has reverberated all day long, but I haven't really heard anyone articulate it as such, and I think I will actually open it up for further comments from the panel or the audience.

DR. SIMON: That was my thought also particularly as I heard Dr. Chambers' presentation. This seemed to me something you couldn't do without a computer-assisted interview process, and although I think the computer is just interview presentations are very interesting in and of themselves in terms of how a blood

center might work, in terms of how they deal with the donor questionnaire, that they were obviously using the current questionnaire, so to really maximize the power of them, I think you have that opportunity to develop something like what you are talking about.

People are doing this, for example, on board questions now, a certain number of questions are answered a certain way, then, they are hooked into a different group of questions, different candidates, and you could do the same thing here.

You start with a general health question and if you get a positive response, then, go to ask about heart, lung--I think there is that opportunity.

DR. LEE: Certainly all the travel questions would lend itself nicely to that.

DR. SIMON: Yes, to harness the computer.

DR. LEE: I think it is possible to do this outside of a computer environment, although a computer would certainly make it easy. For instance, when I registered a book the other day, Question No. 1, "Have you ever registered before?" Based on that, I was able to skip a bunch of questions.

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DR. SIMON: Yes, I think that is true, and we are doing that to some extent in the plasma donor setting where we use a physician or physician substitute, and we ask open-ended questions, and they follow through since they are credentialed training people.

DR. LEE: It is a standard technique of all government forms.

DR. SIMON: But it is easier, I think, with the computer.

DR. CHAMBERS: Actually, one of my handouts is like just a quick off-the-cuff draft of a paper version for a repeat donor that would have the things you have to ask, and then those capture questions, only if they are yes would you flip the page over, and then the supplemental questions are in according to each one of those capture questions.

So, it is doable in a paper mode. I mean obviously, the computer is the perfect way to do it because then you end up with layers, and you can core down depending on the responses, and end up not having to ask a lot of stuff of people because you have already cleared it.

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If they have told you that they traveled, but they didn't go to Africa, then, you don't have to deal with HIV Group O. If they told you that they were born in the United States plus this, plus that, I mean you can build the algorithms that tell you which of the supplemental questions are indicated based on their responses.

I think in a very powerful way, focus them and your questioning to what the real issues are for that person in terms of donor safety.

One feature of that kind of approach, though, is that the questionnaire then doesn't have the specific questions in it that might be in guidance documents. Not every donor is going to be asked have you taken in the last three months the following drugs. I mean if your approach to it is to say don't come to donate unless you are going to tell us every drug you have taken in the last two years, then, you can, by the rules that the health historian has avoid a whole host of questions, as well.

So, the questionnaire looks very different, and if the concept is--and I am thinking in terms of the very

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last presentation, Dr. Cowan's comments about what you might bring that might pass muster--those shortened questionnaires look very lean and mean compared to a standard 45,000 questionnaire, but operationally, they do exactly the same things.

It is not just an additional question, it is a whole different way of getting at the same bit of information, by plucking with big, again, what I call capture questions, but with big nets, getting a net around the subset of donors that has an issue in a particular area and then coning down to the actual individual issue you are concerned with in terms of eligibility.

It means that almost every donor gets asked a different set of questions is one implication, and then how do you prove when all that is done then that you have captured the same group and you have got the same accuracy of response, I think is very problematic, unless we had a gentleman's agreement that something like seeing no difference in the positive infectious disease marker rates would be adequate confirmation that you at least haven't stocked your eligible donor ranks with a bunch of

people who are in the window period or who are seroconverted that you should have been able to identify by history.

There has to be some concrete parameter, otherwise, it looks so different that I think it is almost impossible to have anybody say yes, sure, go ahead and use the blood that comes out the other end of the process.

I am also confused about the realm of possibilities is. I can see problems with putting a lot of effort into something that is one of these sort of computer-based captured and coned down approaches in the absence of knowing what the final proof in the pudding is going to be that will bless that approach as being equivalent or better than what our current approach is.

DR. LEE: Agreed. Thank you.

Dr. Gilcher.

DR. GILCHER: I think that what we are talking about is really the next step with the computer-assisted screening because now we are asking the computer to make a decision, and I think the computer can make the decision, and I think it can make it better than a human

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in terms of the algorithm, because humans make mistakes, but the computer won't.

Every time it will get you into the algorithm, and you will have to do it the same way every time, but that isn't where we are yet, but I think clearly we should be going in that direction. I think we are, but we are not there yet.

DR. LEE: I guess part of the reason why we are not quite there is that everyone expected all the questions to be asked, and the people really didn't think an algorithm approach would be acceptable, but I am clearly hearing from all the presentations today that that is probably the way to go in order to handle this much information in a way that donors can assimilate.

Mr. Healy had a question or a comment related to the subject that we are on now.

MR. HEALY: My question kind of went back to Celso's earlier comments regarding validation, and it strikes me that a lot of this issue turns on validation and how you define it. Yet, there hasn't really been a common definition, and I can think of at least three different things to consider in terms of validation,

whether the questions are understandable, whether they elicit inaccurate response, and whether they are really targeted toward health risks or toward transmission risks.

So, I was wondering what comments the board has, particularly the FDA members, about which of those types of validations might be a priority and whether there is an assumption that the latter, that the questions actually target a health risk, has already been achieved or is assumed to be true.

DR. LEE: Is that directed at anybody in particular?

MR. HEALY: Not, not anyone in particular.

DR. LEE: In the area of validation, we all agree that we need validation, yet, the data to perform the validation is difficult to obtain. To some degree, probably it will wind up happening in a way similar to many blood policies have been shaped over the years, unlike the pharmaceutical industry, the typical pharmaceutical industry, all of the blood rules, policies, and guidelines were not necessarily preceded by

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a randomized, controlled clinical trial on which rational decisions were made.

They simply evolved over time, and they evolved exactly for the same reasons, it was difficult to generate good, practical validation data, yet, the need is there, the need is urgent, the need is imminent, decisions have to be made now. Not making a decision presents more of a public health threat than making a suboptimal decision.

So, in the face of that, you go with what you have. I suspect that to some degree, we will follow that same paradigm. So, in terms of what the FDA will accept as validation data, it all depends on the choices. If it is the best there is, and it appears to be the most prudent step to follow in terms of public safety, that is probably going to be acceptable.

Obviously, I cannot speak as to the outcome of a particular review of an application, but I think that approach cannot be faulted too badly by the public.

DR. CHIAVETTA: Just a comment about the streamlining that we were talking about earlier, and having a simplified version. Over the years with blood

screening questionnaires, I have seen, as we have all seen, more questions get added.

I think we have a philosophic difference that we have to get over at some point. From a regulatory and from a legal standpoint, as a blood service, I want to be sure we are covering all the right topics. Regulatory has to be sure we are addressing all of the known risks.

But that is a philosophic difference than wanting precision in the answer to a particular question. If I were doing an epidemiologic study on whether anybody has ever had Chagas disease without blood tests, let's just say I really wanted to know that, I certainly wouldn't say have you ever had Chagas disease, babesiosis, et cetera, I would never ask a question that way.

Yet, we try to cover so many things because we legally and from a regulatory standpoint, we have to mention the name of certain things, and I think that is a philosophic difference, and at some point when we are doing the streamlining, we do have to come to some agreement about just do we have to mention by name everything when we go ahead.

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I don't know the answer by the way, I am just saying that is something that I continue to see and be puzzled by, because our donor screening questionnaire is not a good epidemiologic questionnaire at all. It is good at coverage, bad at focus.

DR. LEE: Dr. Gilcher.

DR. GILCHER: As the others were speaking, I was making some notes, and I made three notes here. I talked about the amnesiac donor, the ostrich donor, and the purposeful denial donor.

What I meant by that is I think there are some lessons that can be learned. I have had the occasion to go to some of our confirmed hepatitis C-positive donors and actually interview them and say, you know, what was your risk factor, and getting into depth with them, and when I talk about the amnesiac donor, this is the donor who really doesn't remember, they just don't remember something in the past.

Then, there is the person who denies, the ostrich, they really don't want to admit it, but they know that it is there, and then the purposeful donor, and, in fact, that is not what any of the individuals I

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have interviewed have been. They didn't purposefully, I mean they didn't intend to disseminate disease or to transmit disease or to transmit disease, that wasn't their purpose. They are not a terrorist.

I am sharing this with you because in talking to these--and this is just with hepatitis C donors--one of the questions that I found to be most helpful was when I asked them do you have any relatives or close friends with hepatitis C, and they would say, oh, yeah, I do, and then they start remembering the event with close friends where they, in fact, shared the needle.

So, in a sense, what I am talking about is a question that is very broad based, but can then lead you back. We could that with the computer. It would be very hard to do that in a regular donor questionnaire, but it could bring you back, if you were to ask a question like that, do any of your relatives or close friends have hepatitis C, and if they answer yes, then, start digging.

Anyway, I just wanted to share that with you.

DR. LEE: Thank you.

Dr. Bianco.

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DR. BIANCO: Some of the speakers mentioned these, and Dr. Chambers just made a very veiled suggestion, could we use certain criteria for validation, could we say that a change would be acceptable if the prevalence of the infectious disease markers in the donor population of a certain size, statistically significant, of first-time and repeat donors remains the same or decreases, that this would be an acceptable change?

Could we, as we continue doing the REDS study, and particularly among repeat donors, say that if there is no change in the incidence of the markers that you see in that population, say that the changes did not make it worse? This type of measurements maybe could allow us, if were courageous to take the risk in making some of those changes, at least after a short period of time, relatively short, to evaluate them and say yes, they stay, no, they go.

DR. LEE: Dr. Williams.

DR. WILLIAMS: I think it would be excellent to have such a convenient measure available, but I think the problem you run into is that there is enough variance in prevalence patterns seasonally, between centers, between

demographic groups, that (a) you would have to be a model, build a model, and then, secondarily, you would have to see something above and beyond the natural variance, and by that time, you could have a potential problem that you have already contributed to by changing your questionnaire, so I don't think that would be an ideal way to approach it.

DR. BIANCO: Alternatives?

DR. WILLIAMS: Well, I spent 20 minutes talking about the problems without putting forward alternatives. I think the alternatives are very difficult, and I think it is going to have to take some flexibility on both sides, as well as some serious resources to get at some of these issues.

It may demand the large study to change the content of some of these questions.

DR. LEE: Dr. Fridey.

DR. FRIDEY: This is somewhat tongue in cheek admittedly, but I have a three-word answer to the problems that we are confronting, and that is pathogen inactivation systems.

DR. LEE: A topic for another day.

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MS. SIGMAN: This is kind of crazy, but I tend to bring some things to bottom line sometime, and I wonder if, in the consideration of the panel and the task force the next day, that you might consider that in order to look at where we are and where we are going, at the consideration of maybe dropping or changing the oral questions, and stating as a general question, have you been to Central Africa, period, and then going from there, and going into a different layer if anybody has ever been to Central Africa, because that is where you are going to find the oral questions being of a risk factor, and then perhaps, since we have NAT testing, that has closed the window for hepatitis and for HIV, and to the depth it has in the last couple of months in a year or so, if we consider just asking the donor questions, have you ever had hepatitis to see how that correlates with any seroconversions or any window period, have you ever had some of the HIV risk, and considering those three areas as a possibility for validating an abbreviated donor card in the future, because we have done increased testing to, in fact, close the windows for HIV and for hepatitis.

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Also, again, we work in the military blood program, and we probably have a greater depth of donors who travel all over the United States and probably don't even know sometimes where they have been, however, we don't see a great correlation with donors who have been in Central Africa Republic. We defer them, but we are not deferring that many in the military, and yet we have people flying all over the world at different perspectives.

So, I just thought that maybe with our particular donor population and our results and deferrals, that you might consider that that is one of the questions you could abbreviate because I am sure that probably the regular donor population is not as mobile as probably the military one in that vicinity.

DR. LEE: That could be part of the way the algorithm is set up to address a particular donor population.

Go ahead.

MR. MAGAN: My name is Harry Magan, and I am here at the behest of the Canadian Blood Service in Quebec.

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I am on a steering committee--as I am sure many of you, I hope many of you have heard about the donor deferral consensus conference that is planned for next year--probably many of the people in this room are donors, blood donors, but I am here only because I am a blood donor. I am not a blood professional. My entire connection with this whole thing is as somebody who bleeds for other people.

I certainly appreciate what I am hearing here today, and I want to make a couple of comments. I am not addressing questions.

Volunteer blood donors, in my opinion, almost with no exceptions, have no interest at all in doing anything other than good for other people, and I don't think sometimes that that is recognized with the types of questions that are being asked.

I think that donors--and this is not just my own personal feelings, but it is also others I speak to--they don't mind being asked blunt, explicit, very personal questions. What they mind is being asked the same thing time after time after time after time after time. If I have given blood five or 10 or 50 times, and have been

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subjected to those questions, and I haven't figured out that these are no-no's if you are donating blood, then, perhaps I shouldn't be allowed out without somebody to guide me around.

I think, as a blood collection and dissemination industry, ought to have more respect for these people who are the ones who, after all, are getting the holes poked in them, and aren't doing it because they are sick, but because somebody else is sick.

The other thing that I want to mention is it is very gratifying, as a donor, as a frustrated donor, to know that people in Canada and in the United States, who are hopefully, I expect, and I am sure nobody here will argue with me, the cream of the crop of the blood profession, really are trying to do something about it.

I wanted to get a chance to say that before time ran out, and we are already over time.

Thank you.

DR. LEE: Thank you very much.

Any responses from the panel or the rest of the participants?

DR. BIANCO: He's right.

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[Laughter.]

DR. LEE: Gill Conley.

MR. CONLEY: Gill Conley from FDA.

In listening to the discussions today, I just want to put something out really as a general question and comments, given that paid donors have a higher biomarker rate but that has been compensated for with many different techniques within their own agency, given that the FDA, at least right now, the only difference between paid blood donors and volunteer blood donors is the labeling on the product, we don't ask that they be processed any differently, but not knowing how much of a crisis our volunteer donor pool is going to become in the future, we may see more collections of critical products like platelet pheresis products from paid donors.

We are going forward to streamline the questionnaire in a way that I am not sure that it will apply as safely to the remunerated donor as it does to the volunteer donor, and I guess my question is should the task force consider that as an issue as they go forward, should we consider different questionnaires for

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different approaches for volunteer donors versus paid donors.

DR. SIMON: Of course, it is a good question. At least about the data we have now, there is no basis for thinking that one would treat them differently. Now, we do treat plasmapheresis donors, who are paid, differently from whole blood and platelet pheresis donors, but that is largely based on the frequency of their donations, so they do have a much more extensive evaluation with the physical examination, so right now they are getting a more extensive evaluation which may help to pick up things that might not otherwise be picked up.

But at least based on the data we have now, I don't think per se the difference between being compensated and non-compensated would impact on what the question should be, and there is some data from the volunteer sector of incentivized donors with material incentives versus those without material incentives that would tend to support that. But I think it is a very interesting topic for further study.

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DR. CHAMBERS: I think an interesting way to begin to answer that question would be something we were talking about earlier, which was squeezing the post-donation information events, the naturally occurring experiments, to infer where you may or may not have differences in the function of the current questionnaire in terms of weeding out the donors you want to weed out.

I think if you found--take a ludicrous example--if you found that most of the post-donation information where the donor on their tenth donation, for the first time admitted to IV drug use occurred in redheads, then, maybe what you do is you go back and you look at your questionnaire, and you say for redheads, we are going to have an additional question. We are not just going to ask have you been an IV drug user, we are going to ask it three or four different ways at different points in the questionnaire because we know we have a lesion, we know we have for some reason a difficult time getting redheads to self-identify as prior IV drug users.

I would say that the way to reality check the need, then, would be to look at those experiments and see whether there is or isn't a real difference in the paid

donors and the non-paid donors in those post-donation information profiles, and what they do or don't tell you in terms of your questionnaire's efficiency in weeding out people that clearly, you know, it is not a judgment call, they clearly are ineligible as donors and should have been found.

DR. SIMON: We do that, I mean those data are different, but again you have to keep in mind, for example, tattoos and piercings lead the list, but our donors have a physical exam, and one of the major sources of that PDI is that the examiner notices the tattoo or piercing that wasn't noticed a year before that.

DR. CHAMBERS: But the follow up is to ask, I think, Toby, why the donor didn't identify. If they have had the benefit of your video at the beginning, and the questions, you know why didn't they identify it as a problem?

It may be that what you are seeing is the effect of the difference in the demographics. So, maybe the take-home message there is that if you are dealing with a donor under the age of 30, you don't just ask have you had any body piercings, you ask it three or four

different times in two or three different ways, because maybe that is a hard group to get the question to in a way that gets the answer back in an accurate way.

I don't know. I think there is probably just lessons in those errors about the best way to formulate questions and how do to do things like tailor-make them based on the demographics maybe, based on geography maybe, based on the nature of the questionnaire, and the nature of the donor, remunerated or non-remunerated, which I just would put in that category as one of the other variables that might turn out to have some correlation with a certain blip in your post-donation information problems.

DR. LEE: I think we will take one last comment.

AUDIENCE: I was just thinking that that is a pretty slippery slope. If you start finding out that black people didn't tell you that they were using IV drugs or hispanic women didn't tell you that they worked as a prostitute, you have to be careful--or people from a certain country didn't tell you something--you start to get into something that could be a little touchy, and you have to know where to draw the line on that.

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Concluding Remarks

DR. LEE: The hour is late, and I have the dubious distinction of making a few closing comments, and I will try to do so in about 30 seconds.

Once again I would like to thank all participants of this workshop, particularly those sitting at this table, and have presented wonderful information for us to consider, "us" being the entire blood community including the FDA.

I will just try to make four observations, and these are not necessarily agency position, the fact that I am delivering closing comments has nothing to do with the fact that I am from FDA, simply I am part of the organizing group, and no one was really willing to make closing comments.

But here they are. I think much of this has been brought out so clearly that we simply need to focus on them one last time.

The first thing is that we have heard specifically about the importance of donor education, and struggle as we may to improve the questionnaire and the selection process, none of that is going to work very

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well unless we have an educated donor population to work with.

If the donor that comes in, in the door, has a good understanding of what blood safety is and what blood availability is, then, I think we will go a long way, and I think we will find that people's responses are not necessarily so off the wall as we have seen in the past.

So, the question is how do we raise the level of donor insight into the blood donation process, and it is not clear, and perhaps we should broaden our efforts of the Donor History Questionnaire Task Force to include efforts to increase understanding of the blood donation process.

This was not particularly an item in the roadmap that Dr. Fridey showed us, but it is something for us to consider. Perhaps a way to do that is to have an AABB-sponsored, widely accessible web site where donors can log on and freely learn about the process, and maybe even a short mini-quiz at the end of a particular session to test their understanding.

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I don't know, these are some concept that we might consider in increasing the level of donor education.

The second point that was brought out was the fact that we desperately need data, yet data is not forthcoming readily, and it is difficult to get them. It is not clear how to fund these studies to generate the data.

While the efforts are in progress to generate accurate data, that does not mean that we are poised for inaction. We have to move forward with the best information that we have, and given that, if the information is not enough, if the best information is not enough, then, you have to exercise judgment in protecting the blood supply and making sure that there is adequate availability.

The third point that came across very well, at least to me, was the need for an algorithmic approach, and we talked about it briefly during our panel discussion.

I think the goal is not necessarily to slash the number of questions, but to slash the number of questions

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that are posed to a particular donor through a system that recognizes which questions are best suited for that donor, and the way to characterize that donor's need in terms of questioning, perhaps can be identified through a few basic questions up-front.

A corollary to that is the additional technology that is now with us to assist us in better furthering that end.

Lastly, this is certainly a charge not necessarily only for the AABB and the industry, certainly not a charge only for the FDA, but is a charge for us to all as members of the blood community. I am glad that I recognized a particular questioner from the audience who happens to be a devout blood donor. You should really be here answering some questions from the audience, and I thank you for your comments.

With that, I think I will close today's workshop. This workshop has been tremendously helpful. It gives me new insight. I think it is going to allow me to be a more effective member of the Donor History Questionnaire Task Force.

Thank you very much.

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[Whereupon, at 4:35 p.m., the Workshop concluded.]