UNITED STATES FOOD AND DRUG ADMINISTRATION

PATHOGEN REDUCTION TECHNOLOGIES (PRT)

FOR BLOOD SAFETY

PUBLIC WORKSHOP

Silver Spring, Maryland

Thursday, November 29, 2018

PARTICIPANTS:

Welcome:

NICOLE VERDUN, M.D..
OBRR, CBER
Food and Drug Administration

Opening Remarks:

PETERS MARKS, M.D., Ph.D.
CBER
Food and Drug Administration

SESSION 1: Blood-Borne Infectious Agents and Their Impact on Blood Safety:

SIMONE GLYNN, M.D., MPH, Moderator
NHLBI
National Institutes of Health

Risks to Blood Safety From Infectious Agents:

MICHAEL BUSCH, M.D., Ph.D.
Vitalant Research Institute

Pathogen Reduction: An Overview of Policy Issues:

STEVE KLEINMAN, M.D.
University of British Columbia

Pathogen Reduction Technologies for Platelets: Current Status in the United States:

EDWARD SNYDER, M.D., FACP
Yale University, Yale New Haven Hospital

PRT for Plasma in the United States:

JAMES AUBUCHON, M.D., FACAP, FRCP (Edin)
Bloodworks Northwest, University of Washington

PARTICIPANTS (CONT'D):

Panel Discussion:

MICHAEL BUSCH, M.D., Ph.D.
Vitalant Research Institute

STEVE KLEINMAN, M.D.
University of British Columbia

EDWARD SNYDER, M.D., FACP
Yale University, Yale New Haven Hospital

JAMES AUBUCHON, M.D., FACAP, FRCP (Edin)
Bloodworks Northwest, University of Washington

SESSION 2: Implementation of Pathogen Reduction Technology for Blood Products in the U.S.:

BILL FLEGEL, M.D., Moderator
NIH Clinical Center

Experience Implementing PRT:

DAVID REEVE, MBA, MHA
American Red Cross

PRT Implementation in a Hospital-Based Blood Center & Acceptance by Hospital Staff:

BILL FLEGEL, M.D., Moderator
NIH Clinical Center

Impact of PRT on Platelet Quality, Count, and Clinical Implications:

DANA DEVINE, Ph.D.
Canadian Blood Services

Considerations for Implementing Solvent/ Detergent-Treated, Pooled Plasma Into a Hospital System:

PARTICIPANTS (CONT'D):

CLAUDIA COHN, M.D., Ph.D.
University of Minnesota

Health Economic Considerations for Pathogen Reduction Technologies:

BRIAN CUSTER, Ph.D., MPH
Vitalant Research Institute

Panel Discussion:

DAVID REEVE, MBA, MHA
American Red Cross

DANA DEVINE, Ph.D.
Canadian Blood Services

CLAUDIA COHN, M.D., Ph.D.
University of Minnesota

BRIAN CUSTER, Ph.D., MPH
Vitalant Research Institute

SESSION 3: Pathogen Reduction Technologies for Whole Blood and Red Blood Cells:

RAYMOND GOODRICH, Ph.D., Moderator
Colorado State University

Optimal Pathogen Reduction System for Blood Safety: Is It a Dream?:

RAYMOND GOODRICH, Ph.D.
Colorado State University

Clinical Experience With Pathogen Reduction for Red Blood Cells: Completing the Trial:

RICHARD BENJAMIN, M.D., Ph.D., FRCPath
Cerus Corporation

PARTICIPANTS (CONT'D):

State of PRT for Whole Blood:

ANNA RAZATOS, Ph.D.
Terumo BCT

PRT of Red Cell Products: Impact on Biochemical and Viability Parameters in Humans:

JOSE A. CANCELAS, M.D., Ph.D.
Hoxworth Blood Center, University of Cincinnati

Panel Discussion:

RICHARD BENJAMIN, M.D., Ph.D., FRCPath
Cerus Corporation

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Terumo BCT

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Hoxworth Blood Center, University of Cincinnati

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P R O C E E D I N G S

(8:04 a.m.)

DR. VERDUN: Good morning. I think we're try and get started because we have a very packed schedule. So good morning. My job today is to welcome all of you. We're very, very excited to have everyone here. So on behalf of FDA, CBER and the Office of Blood Research and Review, welcome.

At the core of our mission and the office is the safety, obviously the safety of the blood supply. And so this pathogen reduction technologies for blood safety really gets to the core of our mission.

And we're quite excited that all of you are here to participate. We are hoping that this will foster innovation and discussion and move things forward in terms of safety. That is really at the core of our mission and our goals.

I'm doing to do something a little bit unusual this year at this meeting. And I'm going to do acknowledgements up front because we have a

lot of people that really worked quite hard to put this together.

And I really would like to first acknowledge CD Agrea. So, thank you CD for spearheading this and for putting this together. He really took sort of an idea and put it all together and made it happen. So I really would like to say a thank you to you for that.

In addition, CBER organizing committee. We have several external advisors that are listed on the slide. And also several people that helped to support the travel and otherwise as listed.

So again, thank you all for being here. I'm going to turn it over to Dr. Peter Marks for some opening remarks on pathogen reduction technologies for blood safety. And thank you.

DR. MARKS: Thanks very much again. We really appreciate everybody traveling here. This is obviously a very important area to our center.

Blood products are potentially lifesaving for a variety of different acute and chronic conditions. And those range from people

who have experienced trauma, trauma victims, to supportive care for cancer patients.

However, transfusion-transmitted infections remain among the most significant potential complications of blood transfusions, despite major advances in risk reduction that have been accomplished by a combination of donor screening and laboratory testing.

Year round global infectious risks include hepatitis B, C, and HIV. And local risks include West Nile virus and Babesia, and obviously there are a whole host of other pathogens that I haven't mentioned.

And for platelets arrived from whole blood or by apheresis, which are generally stored at room temperature, there is the issue of bacterial contamination risk.

So although testing can mitigate the risk of transfusion-transmitting infectious diseases, it comes at both a cost and it's not perfect.

In addition we have continually emerging

pathogens which continue to challenge us to put in place new testing which, obviously, brings with it associated costs and, again, challenges the blood supply.

So pathogen reduction technologies address this risk or aim to address this risk from viral and bacterial pathogens. But current technologies, which tend to use either a nucleic acid binding agent and ultra violet light, they are -- although a significant advance, they are yet to be perfect.

And that's because they either have inadequate inactivation of certain pathogens or because they lead to decrement in product yield, or because they can't be used on whole blood, which could then be separate into all the different components.

So we think that, at least, and we look forward to having discussion today. At least our thinking is that the ideal pathogen reduction technology would be able to be performed relatively simply on whole blood, would allow that

whole blood to be separated into the various components, much in the way that it is currently into -- in current practice minimally disrupting current blood banking practices.

And it would also then lead to an activation of a very broad array of DNA and RNA viruses. We know that no technology is going to technology is going to get everything. But we'd like to see something that could get the majority of things that would ultimately potentially allow us to start to conceive, think about starting to peel back off of the viral testing which we do, and bacterial testing which we do on products, which would then allow us to just try to get to a place where it was a cost-efficient or potentially even cost- beneficial intervention.

So given this importance to public health and to the safety and availability of the blood supply, our center at FDA really wants to work with a variety of stakeholders to advance this technology.

And we look forward to working with all

of you over the coming years to try to advance pathogen reduction technologies to really hopefully bring us to a place where we have the kind of a blood supply that is protected against pathogens that emerge like the next Zika virus without having to scramble to put in place testing because we feel confident in the ability of a pathogen reduction technology to protect against those pathogens.

So thank you again. We look forward to a robust discussion and we will obviously after this workshop, we'll be following up too.

So thanks again.

DR. GLYNN: Good morning. My name is Simone Glynn. I'm from NHLBI. And I have the privilege of being the moderator for the first session, which I think is going to be quite exciting.

I'm going to ask the speakers from the first session to come up to the table in the front there.

The other thing I wanted to let you know

is that we will reserve all of the questions, whether they are provided online or from the audience, for the panel discussion which is supposed to be about 9:50 or so. So if you can hold onto your questions to the end.

So our first speaker today is going to be Dr. Michael Busch from Vitalant Research Institute. And he is going to talk to us about the risks to blood safety from infectious agents.

DR. BUSCH: Thank you Simone. I appreciate the opportunity to present. My talent is the former blood systems. We rebranded. And we have a fancy new color. See if it comes up.

Is that working? Thank you. That's our new color. Great. So this should go to full screen.

So I'm going to move swiftly. We did just complete with Steve Kleinman and Evan Block a review of this areas. So we'll be published soon in blood. So disclosures, you have funding from NIH, NIVC to accept commercial relationships with a number of companies over the decade. So, all

listed here.

Just a general principal, which is we've moved from a period back in the '80s, when I first started getting involved in with blood safety, where we could actually directly measure risk either through going back to samples or following recipients and retrospectively determining rates of infection to a brief period in the '90s where we could actually directly measure risk with large-scale studies because the risks were high enough that we could quantify the frequency of infections in zero-negative units.

But now we're really in a period of modeled risk. So over the last now close to 30 years, all of the estimates for residual risk that we'll be talking about are estimates based on modeling.

And just to walk you through a little bit of that, this is work, you know Harvey Alter and Harvey Klein dating back to the '70s had large cohorts of prospectively-followed transfusion recipients at NIH.

There were similar studies led to Jim Mosley, the TTVS cohorts, where they measured the rates of ALTL elevation, hepatitis occurring in recipients. And they were observing rates as high as 33 percent of recipients of multiple units acquiring elevated enzymes consistent with transfusion hepatitis.

At the time we began to discovery viruses. So hepatitis B surface antigen. Australia antigen was discovered and implemented. And immediately there was a dramatic drop with implementation of hepatitis B first generation testing.

But the other observation then was that the rates of hepatitis surface antigen were much higher in paid donor in other populations: prison donations that were allowed at the time.

So this led to the introduction of assention of all volunteer blood supply, and a dramatic risk not only in the rates of hepatitis B, but also an unexplained elevated liver enzymes, so-called non-A, non-B hepatitis.

And then over the ensuing decades in 1989-1990, hepatitis C was discovered, and progressive improvements in hepatitis C antibody. And then eventually nucleic acid testing for HCV, essentially eliminated risks.

So in the last nearly 15 years, there has not been a single case of post-transfusion hepatitis discovered in the ongoing program here at the NIH. So incredible success in eradicating classic post-transfusion hepatitis.

Similarly, work in did HIV in San Francisco modeling back from the rates of infection observed when we first started to save samples in the mid-1980s as part of the TSS. And then looking back overtime at rates of donations we were able to, from gay men and HIV infection, to model the risk of HIV prior to screening.

And that risk peaked at well over one percent in San Francisco per unit before the first transfusion AIDS case was reported in San Francisco in late 1981. So that led to implementation of self-deferral and progressive

enhancements in deferral from just very high risk MSM to all MSM, and then finally to introduction of screening.

So this is another example where deferral of high risk populations led to a dramatic reduction, nearly tenfold in the risk of transfusion HIV before testing was actually available for this specific agent.

So similar with hepatitis C we virtually reduced risk of hepatitis tenfold before the test was available. So strong evidence continued support for the concept of pillars of blood safety, including selection of the safest possible donors.

Now once we implemented screening, this is again specific data to San Francisco, we had fairly high rates of infected donations. So when you first start screening you can really impute that the rate of positivity when you start screening reflected the risk immediately prior to screening.

And we were seeing nearly 1 in 400

donations were positive for HIV. The vast majority of those were from men who have had sex with men.

But over the ensuing just four or five years, a dramatic reduction in the rates of positivity due to both culling out of repeat positive donors, but also progressive improvement in self deferral measures, and a movement toward what we see today, which is a much broader risk of risk factors in infected donors: a combination of still some level of MSM, but also heterosexual risk drug use.

We did do some large studies funded again by NHLBI. There was a big study in San Francisco, and then a large study led by Ken Nelson in Houston and the Baltimore Hopkins area.

The study in San Francisco actually involved taking samples of PBMCs from zero negative donors and doing pulled cultures in PCR. And a very large study of 75,000 donations ended up with one positive pool.

And so a very low yield, very expensive,

and onerous kind of study to actually do that kind of large-scale PBMC separation and culture and early PCR technologies. But just illustrating what was the realization that we would no longer be able to directly measure risk.

So these points here in this box represent that last direct measures of risk either coming from studies like I just described to pulled-culture PCR technique, or the large-scale studies done in Houston and Baltimore, where they followed recipients and measured the rates of serial conversion.

So this was linked, obviously, to the introduction of testing, but did show evidence of declining risk. And this really transitioned us into the current era of modeled risks.

I just do want to mention though that in the late '80s early '90s, there was consideration of peak-24 antigen testing, so there were also some very large-scale studies, one led by Harvey Alter, that screened 500,000 U.S. donations for peak-24 antigen under the theory that peak-24

antigen could interdict window-phased donations.

And a second study that I was involved with where we went back to a repository from the transfusion safety study. We focused on high-risk populations: men living in zip codes with high rates of HIV. So it was the equivalent of about two million donations.

But there were no antigen-positive, antibody- negative donations detected. So again, very large, expensive studies with zero yield. So further evidence that the approach of direct measurement of risk was really no longer viable.

And this led to a group of us stepping back and saying why are we still concerned about risk if we can't even measure it. The biggest issue, as we'll talk about in a fair bit of detail, is the concept of the window period, that people are donating blood after they have become exposed and infectious as a transfusion -- as a blood donor, but before the screening tests are positive.

There was also concern, and there were a

number of studies, big studies: New England Journal paper reporting that people were infected with HIV or other viruses and yet never formed antibodies. And at the time we were relying on serological tests for mostly antibodies. So so-called immunosilent infections.

There was also the theoretical possibility of testing errors. That the tests simply failed either due to not performing them correctly. At this point early in the '90s we were still with fairly manual testing platforms. Or due to inherent test design problems.

And then viral variance. We knew -- began to appreciate that many of these viruses had different subtypes and quasi species. And the concern over strains that could evolve, that might not be detected by the current generation tests.

So what we realized as we began to study this was that the real problem was the window period risk. And we'll go into some detail on that. A number of studies were conducted that essentially disproved the principal of

immunosilent carriers, people who were chronically infected but failed the serial convert to HIV or hepatitis.

Testing errors. There were studies does that showed that especially as we moved to the more automated platforms and with redundant, in many cases, serologic and now molecular testing, that the concern over testing errors is really not a problem. And I think we've now accepted that the test platforms we're running are extremely robust.

And viral variance, they do exist. And they continue to emerge. So are a combination of viruses all over the world. But in the U.S. these variants are really extremely rare. And as I'll show at the very end for HIV, but for the other viruses as well, the rates of variant virus is very rate and stable in the U.S.

So in terms of the real risk, it's coming from the window phase, from people who are infected but still not positive by standard markers. So in order to estimate the residual

risk, the concept of the incidence rate window period model evolved.

And this allows you to both calculate residual risk as well as project the yield of improved assay. And the requirements in order to measure these parameters are that you need to know the incidence rate: the rate of new infections in your population.

And we talked about adjusted incidence rate here because there is an incidence rate you can observe and repeat donors, of rates of serial conversion actually directly observed.

But we also have to calculate the rate in first-time donors and then adjust the overall incidence in repeat donors to account for the fact that first-time donors also have potentially a higher incidence. And we have approaches to do that.

The other issue is to understand the duration of the infections window period. How long after exposure does it take before there is an infectious viremia? And then how long is that

infectious viremia prior to detection by the currently-available markers. So this concept of an infectious window period.

And when you multiply the duration of the infectious window period times the incidence rate, you can calculate residual risk.

If you want to know how much gain will we get by adding a new test, PCR or molecular technology, you can simply multiply the adjusted incidence rate times the difference in the old versus the new test and predict the rate of new infections.

Now this concept of an infectious window period really was framed out very nicely in a study that was led by Lyle Petersen, who many of us know as the arvo virus director for the CDC. But at the time he was running a very large CDC-funded population study of infected blood donors.

And Lyle did an analysis with Glenn Satin and a number of people here in this room where he examined the rate of serial conversions in donors. And there were a total of 179 donors

who serial concerted for whom the recipient outcome was known, whether the recipients of a prior serial negative donation became infected or not.

And then when they analyzed whether the recipient became infected relative to the inter-donation interval between the zero positive and the prior negative donation, there was a really dramatic relationship.

So three quarters of recipients who got blood from a donor who had serial converted within three months became infected. Whereas you went out beyond a year, virtually none of them became infected.

So by modeling this relationship, what Lyle and Glenn Satin were able to do was to calculate the length of the infections window period with the earliest available assays. And that was quite long. It was almost two months.

So demonstrating that although we thought we had pretty decent tests back in 1985, there was actually a residual two-month infectious

window period.

So fairly large numbers of recipients of zero- converting donors prior to donations became infected, particularly if they got units that were collected fairly shortly prior to the donation that was positive.

They did how in the paper that if they restricted the analysis to the later time period that the window period seemed to have been reduced.

So at that point our group, as well as others, began to really look at zero conversion panels. These are plasma, frequent plasma donor panels, and quantify the time between detection by different assays.

And in this early study we could show that the improved HIV antibody test could reduce the window by about nine days. A next generation test could detect IGM by 20 days. And then by doing direct virus measures, antigen DNA or RNA, you could reduce the window period by about a month.

So early work that led to a principal which is really true for all the viruses, which is that -- and all the infections, which is that we go through these period of acute viremia, detected either by molecular technologies for RNA or DNA, then potentially direct antigen detection.

And then depending on the antibody assay configuration, you can pick up the early IGM stage with so- called third generation or progressive IGG with different generation antibodies.

So this led to the concept of closing the window period by implementing more sensitive tests. And we've moved again from tests that took about two months to zero convert to tests with antibody that took about three weeks.

And then the further closure of the window period with nucleic acid testing down to potentially as little as 11 days with ID-NAT.

Just one point that this whole principal that came from blood banking. How can we close the window period? How can we protect patients? Led to the concept of staging of HIV infections,

the so-called Fiebig staging which uses cross sectional testing strategies to determine where people are in the progressive evolution of HIV infection.

And this is widely used around the world to categorize HIV-infected people as to what stage of infection they are when you pick them up so you can make decisions about treatment and pathogenesis.

Now, in terms of infectivity, it's a very complicated issue because there are a lot variables that influence whether a person is infectious from a blood transfusion perspective after they've been exposed.

And, of course, many exposed people don't get infected. So we're really particularly focused on people who are exposed and eventually will prove to be infected. But a lot of viral properties, the genotypes, the viral load, the stage of viral infection.

Is antibody present that might neutralize infectivity? Contusion factors in

terms of the duration of storage of the component. Whether there are co- trantusions of other zero positive units for some viruses, or people who have had HPB vaccine. Those could neutralize.

And then the recipient factors. Just the underlying health of the recipient, immunosuppression status. Sometimes recipients lack receptors for certain viruses. They may have immunity either from prior exposure or from vaccinations.

So there's a lot of variables that influence the infectivity. And then there's approaches to try to quantify that infectivity that range from in vitro systems. A lot of work has been done with animal models, early on hepatitis B and C in chimpanzees were done. Very careful dose escalation studies to define the minimal infectious dose.

We want to learn as much as we can from human data, from human look-back cases. And I'll show some examples of that.

And then when possible, to actually do

prospective transfusion studies, systematic studies where you enroll large numbers of donors as we look at emerging agents and we can't screen yet but we can potentially do prospective studies. And I'll illustrate that.

This has led to examples like this of the models, not only of the dynamics of the viral load, but the probability that these units that are given and are transfused from individuals in various stages of infection are infectious.

And there are periods where the infectivity is quite low or even non-existent because the eclipse-phased concept, that there is a period shortly after exposure when virus may not be in the peripheral blood. It may be replicating locally in the dissemination -- in the inoculation side.

So there's concept again laid out here. And again, there's a review is cited here.

So this is data from the Red Cross that Roger presented at the recent ABSA meeting that sort of puts this together. This is really nice

results over about a decade of the fairly recent past of the incidents of HIV in repeat donors in the Red Cross showing a fairly low incidence that seems to be progressive declining over time.

And then combining that with the latest estimates for the infections window period of about nine days for HIV, seven days for hep C. And with progressive improvement of HPV NAT assays down to as little as 18 days for HBV.

And what you can see is in the most recent periods, we're not dealing with risks, residual risk estimates in the range of $1-2 to $1-3 million. So 1-3 million transfused units.

So really testing has been extremely successful at reducing risk to extraordinary low levels for these agents for which we have excellent tests, in combination typically of serologic and molecular technologies.

Now these estimated risks are quite a bit higher than the observed rate of breakthrough infections. And there are many reasons for that. Obviously a lot of patients are very sick and die

of underlying disease.

Most of these cases of breakthrough infections are found to look back. And that requires that a donor come back and zero convert and then we can trace the recipient.

This was data published by CDC back in 2010. You can see that these were essentially the data that Lyle Peterson had analyzed where there were every year 15 or so people who were documented to have acquired HIV from transfusion following a donor zero converting.

But over the subsequent decade or more, there were a handful of cases. And then subsequent to that, there were really just a very small number of cases reported in the U.S. And Red Cross has a more recent compilation. Every couple of years we document a breakthrough HIV transmission case.

But if you step back and look globally, which is this slide obviously too busy to see in any detail. But on a global basis, there have been about 30 transmissions of HIV from

NAT-screened blood. What we call NAT -breakthrough infections.

Several of these were due to test failure, with the test not being able to detect variance. And now FDA and almost the world requires dual target testing. So you have to detect two different regions of the HIV genome in order to prevent failure of tests to detect a variant.

The majority of the rest of these were from mini- pool mat. So there's really only one case reported from South Africa where an ID-Nat screen unit was implicated in transfusion transmission.

And if you put all this data together and you try to model what the minimal infectious dose is of an RNA positive antibody negative unit that would be missed by NAT, mini-pool NAT, it's really quite low: about 50 variance in the inoculum. So the virus is really quite infectious during that acute ramp-up phase. And we are, obviously, still seeing it low rates residual

transmission, particularly in mini-pool mat.

And to expound on that a little bit, this is data from (inaudible) Marian Vermeulen and colleagues looking at the viral load distribution in South Africa of window-phased donations.

So these are antibody negative donations that were picked up by ID-NAT. And you can see some of these would have been detected by a P24 antigen, but the majority were RNA only.

And of those RNA only samples, a fair number of them were quite low viral loads. They were only quantifiable by replicate testing. They were below the limit of quantitation of viral load assays.

And it's these low viral load samples which are probably infectious that are the concern. And in this analysis what Marian did, because in the U.S. we still run mini-pool NAT. They took samples from these low viral loads and they ran them in replicates on either the Ultrio or the Ultrio Plus or the tax screen so that the Grifols or the Roche assays to ask what proportion

of those would have been missed had they done small pools.

What you can see is of those low viral load samples, you would have missed about 20 percent of them had you done mini-pool NAT. So we have to recognize in the U.S. we're still running mini-pool NAT. Mini-pool is a six with Roche. Mini- pool is a 16 with Grifols.

So we're missing some fraction of these low viremic units. And this is one reason why you would be interested in PRT, to really safeguard against these low viral load units.

Now this is a proportion of a very small number of positive donations. So, as you'll see, we only pick up a handful of NAT yields per year. So we're only missing maybe one or two per year due to the fact that we're still relying on mini-pool testing.

Now moving from the established viruses to the emerging viruses, you can see here that as we're driven down the risk of HIV, hep B, hep C, to non-quantifiable directly, but theoretically

risks in the range or under one a million, we've been struck with an onslaught literally every year of a new emerging agent threat.

And some of these have proven to be significant pathogens. We'll talk a little bit about that. Many of them have not. And again, what's changed is the classic pathogens, hep B, hep C, HIV, HGLV, they are chronic persistent infections.

We've got this window phase, but then almost everyone who gets infected has a chronic low-grade infection, asymptomatic, mostly sexually or IDU transmitted, and clearly cause severe disease.

But the new agents we're worried about, most of them cause very transient infections. Most of them are zoonosis that are coming from animals into humans. Many of them transfusion transmission is not well established.

A number of them, as we've studied them we realize that they don't cause disease. So it's a whole different mindset as we think about these

emerging agents that we're responding to.

And recently following ZICA, we wort of step back and we developed this concept of how do we study these agents. And again I don't have time to go into it in detail, but especially once we've got a test and we begin to look and try to find infected donors, we can really enroll those donors and characterize the kinetics of viremia, the infectivity of that virus, really directly measure incidents, prevalence, build repositories to help evaluate performance of tests and improve performance of tests, do in vitro and animal model infectivity studies.

So we sort of have a road map now as a new transfusion emerging agent is discovered or alleged. We have a systematic approach to study that.

One example we're noting is XMRV because it was a huge concern. This was a paper published in Science that alleged that this new xenotropic murine leukemia-related virus, XMRV, first discovered with the array the Virochip as

associated with prostate cancer.

But in this paper from Judy Mikovits, they alleged that this was frequent in patients with chronic fatigue syndrome. And a control group of blood donors showed that four percent of asymptomatic healthy blood donors were allegedly positive for this XMRV virus by PCR culture.

And this led to a blood working group with FDA and NHLBI. It led to two years of extensive work. Millions of dollars spent to develop studies, build panels, distribute these panels to dozens of laboratories to investigate whether this XMRV association with chronic fatigue syndrome and particularly transfusion risk was real.

And the bottom lie was it was all false positive. There was contamination by an in vitro recombinant virus, not even a human virus. So really a lot of work to disprove a false alarm.

And there have been a number of these fake news events. So a number of these items I showed you proved to not be real problems,

vis-à-vis transfusion safety.

So we have to be very careful, especially in this era of metagenomics where we are discovering viruses all the time to not over react. And this is where, again, PRT would give us more time to not be fearful, but rather do the systematic studies to understand are these real.

Now I'm not going to go into detail, but I just wanted to mention some of the major real problems that we did deal with over the last 15 years. Variant CJD obviously resulting from the mad cow syndrome.

A problem in the UK. A very fatal, horrendous disease. A contusion transmission threat was observed early on and subsequently proven. There were a handful of transfusion cases that were documented. There were no real interventions so although there have been efforts to develop tests and filters, these have not proven to be viable technologies.

So the FDA took the position that this required intervention. And they systematically

evaluated the risk of deferral of individuals who had lived in the UK and other regions and did implement deferral policies that we are all familiar with, which led to about a three percent loss in our donors.

Now we, more recently, have pretty much proven that there is no second wave due to a genetic variant that many people have that could have resulted in a second wave. So we are seeing a progressive relaxation of those deferrals.

Chagas disease. Obviously a huge problem in Latin America. A number of imported cases in the U.S. led to a decision to implement antibody screening in 2007.

The initial screening was universal testing of every donation, but then work, again led by Sue Stramer and paper is in press now reporting the results of a large incident study as well as ongoing surveillance of first-time donors have established that we can really rely on one time donor testings.

So every donor is tested once. And the

80 percent of donations from repeat donors do not need to be rested. And this has really been a successful strategy that has led to complete interdiction of transfusion transmission of Chagas over the last ten years.

West Nile virus was a huge real problem. So, again, it entered the U.S. in '99 in New York, spread quietly in the east coast for a few years, but then in an explosive outbreak in 2002 with thousands of neuroinvasive cases, 23 cases were reported of a transfusion transmitted West Nile virus.

So we implemented mini-pool NAT using the platforms that we had established for HIV, hep C, hep B. And that was a very rapid response. Within six months of the realization of transfusion transmission, we were screening the blood supply with mini-pool NAT.

But we realized that the mini-pool NAT was missing low viremic units that were transmitting. So there were 14 breakthrough cases. And that led to the targeted ID-NAT

strategy which has been so effective, essentially eliminating West Nile transmission.

We do detect hundreds of West Nile infected donors every year. So clearly a great example of a successful testing strategy.

Dengue became a concern in part because there were case reports beginning to come from particularly Asia. So Hong Kong and Singapore had read clear transfusion transmitted confirmed. There were zero prevalence studies that were done in Puerto Rico and Latin America that were showing that one or two percent of donors during large outbreaks were seasonally occurring were viremic for Dengue.

So this led to NHLBI launching a study as part of the Reds III program of transfusion transmissions in Brazil. And this study took place in Rio de Janeiro. Brian Custer, who is here, and Esther Sebino led this study. It just shows you the kind of scope of the studies that need to be done and optimally done where these epidemics are happening.

So about 50,000 donors were enrolled and consented. And their samples were tested for Dengue RNA. About 1,000 recipients were enrolled and pre- and serial-post transfusion samples obtained. And overall this study led to testing all these samples and determining that about one-third of recipients of Dengue RNA-positive blood became affected.

Ciril converted became viremic for Dengue, so all of these recipients though were pretty much asymptomatic. And there was absolutely no difference in the rate of Dengue-related symptoms in the recipients who got Dengue from transfusion versus control recipients who didn't get Dengue. Or two times as many recipients became infected with Dengue from community-acquired infection as became infected from transfusions.

So when you're dealing with these kinds of outbreaks, a lot of infections are happening from that setting.

So Babesia is another problem we're

dealing with now. Initially IND testing was done on antibody and DNA. But now we're moving to DNA only INDs. And a beautiful piece of work again by the Red Cross showed that by screening blood you could essentially prevent transfusion of Babesia. Whereas if you had regions that were not screened, there was still residual risk. So we're clearing moving to introduction of Babesia testing.

Zika virus. Again, we're all very familiar with that outbreak. The rapid decision by FDA to drive testing first in Puerto Rico and then nationwide with substantial cost. So quite a controversy. But the real surprise to many of us was the virtual disappearance of Zika over the subsequent two years.

So we had this massive outbreak in South America, Central America, and the Caribbean islands. And yet over the last two years, there has virtually been no cases either identified through donor screening or through clinical case ascertainments. So unclear reasons and just illustrating the unpredictability of these

outbreaks.

This was the outbreak in Puerto Rico detected by donor screening. So very rapid implementation in April of 2016. First day five positives. Peak rates of almost two percent. 369 infections interdicted. This was with the Roche Cobas assay.

But again, over the subsequent two years, zero yield. Most of these donations were very high risk. They were zero negative. And they were mini-pool detectible. Some were ID only. So when we did simulated mini-pools they were IGM negative and only detectable by ID NAT.

And again, extensive work on the infectivity. These are probably highly infections units with high viral loads. In contrast, in the continental U.S., the yields that were picked up tended to be what we call tail-end infections. So they were already zero positive, very low viral loads, mostly travel acquired infections.

And just to show that despite this massive epidemic, if you do zero surveys before,

through the course of, and after the outbreak you can actually determine the proportion of the donor population infected in the context of a very large outbreak based on that yield.

And this is showing new data where when we went back to 500 samples collected a year before the outbreak, virtually no zero positivity. By the time we started screening, and this is I think an important point, already four percent of the Puerto Rican donor population had been infected by the time we started screening. So just showing that no matter how fast we start, you can break through.

But the peak was around 23 percent. So there is still a lot of susceptible people in Puerto Rico to Zika.

In the continental U.S., the yield was small but significant. Again, mostly travel acquired infections. Again, data from the ABB website and Sue Straymer's group. And Sue had a New England paper last year that documented the rates of infection in the Red Cross system. Huge

numbers of donations screened. Huge cost with relative low yield.

This is just showing the infectivity in Macaques. And you can see that with knockout mice that are highly susceptible, as few as 10-20 viruses will transmit. Whereas with Macaques, you actually need thousands of copies of Zika to transmit. Which probably explains the disconnect between the rates of viremia and the small number of transfusion cases that have been reported.

I'm just going to close by highlighting a program that FDA has launched in conjunction with NHLBI and the Health and Human Services. This is a program that's called the TTIMS, Transfusion-Transmissible Infections Monitoring System.

And it has two major components. One is the database management system run through Red Cross and Sue Straymer. PI the other laboratory and risk factor program led by Brian Custer. And these are monitoring the U.S. blood supply with about 60 percent of the U.S. blood supply being

tracked for rates of infection, prevalence, residual risk, extensive laboratory characterization of these infections.

So a really very robust prospective system for monitoring the blood supply. Data consistent with Red Cross's latest data on overall prevalence rates of each of the viruses, incidence rates down in the two per 100,000 person years, so quite low, and residual risks in the one in two million range.

So this systematic program is now in place and is expected to continue for the foreseeable future. This is just looking at the NAT yield rates. As I mentioned, we really only pick up a small number of HIV NAT yields per year, slightly higher numbers in the range of 10-15 HCB NAT yields and low rates of HBV NAT yields. So an approach to measure incidents directly through NAT yields.

And just the last bit of data which is the rate of recent infections among your HIV positives. By performing testing for recent

assays we can determine the proportion of infections that are recent. And you can see how stable that's been, at very low rates.

And just to then finally close by saying that this is all of the testing that's been implemented over the decades. So incredible investment in testing with incredible incremental cost linked to that testing that have not been sustained in terms of pricing over the last few years.

And again, the last slide from this recent review just that you can come back to later that just shows the risks of all the agents over time.

And with that I'll close just by acknowledging the Reds Group, Reds I, Reds II, the Reds III team that have been involved in all this, and then the TTIMS group that I alluded to at the end.

Thank you.

DR. VERDUN: Thank you very Mike. This was an excellent review. And we have lots of

infectious agents to worry about. That's for sure.

So I'm going to ask for the next speaker to come to the podium. So this is Dr. Steve Kleinman from the University of British Columbia. And he is going to talk to us about pathogen reduction, an overview of policy issues.

DR. KLEINMAN: Thanks Simone and thanks to the organizing committee for inviting me today.

So my task today is really to give a number of different observations, ways to think about pathogen reduction that I hope will reverberate through the meeting so that we can discuss all of these points. I'm sure others, Peter kind of alluded to some of these points initially. And I'm sure other speakers will expand on many of these.

As I said, my talk won't be as data rich as Mike's. It never is I think. But I will try to focus on some policy issues.

(Recess)

DR. KLEINMAN: Sorry for that delay.

Initially some disclosures. I'm a consultant to Cerus, which is the manufacturer of the intercept pathogen reduction system, on the medical advisory board of creating testing solutions, but the views expressed in this presentation are my own.

So first the definitions. The broad definition of pathogen reduction: any techniques used to reduce the load of viable pathogens transfused. And of course even physical removal by filtration will result in pathogen reduction.

But obviously what we're really talking about today is pathogen inactivation using a combination of chemical and physical agents. And I think the right terminology now is that we have pathogen inactivation technology that results in pathogen reduced blood components. So that's how I'll be using the terms.

Just a bit of a historical background to kind of summarize I think a lot of what Mike had spoken about. I break, at least from the time I started in transfusion medicine in the early '80s, I break the last three decades down into three

periods.

We had the pre-HIV period which was prior to 1985 when we knew there were significant risks of transfusion transmitted infections. But the clinical significance of these risks were in some ways minimized and certainly interventions were relatively slow to be implemented.

And then with HIV emerging in 1985 and probably lasting for the ensuing 15-20 years, interventions to maximize blood safety were given very high priority almost without regard to cost. Now, this probably came at least in part from the legal and political consequences of HIV transfusion transmission and how decisions were made both in the U.S. and elsewhere in the world.

And during this time period when we were looking for the most robust blood safety interventions clearly new techniques were developed and that's when we got our high throughput nucleic acid testing instituted. And during that time the concept of pathogen inactivation was seen for blood components was

seen as a very important goal that of course everybody would want.

But now we're in the post post-HIV era. And the safety paradigm is a little bit less clear. I think most people are on the wavelength of talking about tolerable risks. That is, we realize we can't reduce risk to zero. But they were also talking about tolerable costs because of the economic situation, especially in the blood industry, but also in medicine in general.

And during this post post-HIV era, we also have great techniques for pathogen discovery. And so we've had an accelerated rate of detecting emerging infections agents as Mike has just discussed.

Now everybody in this room knows that plasma manufacturing sector that makes plasma derivatives has been doing pathogen inactivation for 30 years now. And there have been no reported transmissions of HIV, HBV, or HCV by a pathogen inactivated plasma derivative since 1987 when the measures became more robust as they are today.

Interestingly, 15 years later when West Nile virus emerged, the inactivation methods provided similar protection and they've continued to do so for most emerging infectious agents.

So based on this positive experience in that sector, it seems reasonable to apply this same safety paradigm to blood components. Now there is a difference obviously. One infected donor whose plasma goes into a manufacturing pool can infect many recipients whereas in blood component production, if we make two or three components we would only infect three recipients.

So you could argue that it was more important to do this for plasma derivatives, but nevertheless, you have to ask the question if we can do it for plasma derivatives, why shouldn't we do it for whole blood components.

This was alluded to by Peter, a conceptual approach for pathogen inactivation. First is we take whole blood, divide it up into its various component types, or we start with a component like platelets that we collect by

apheresis and we treat that component.

And this may be suitable for countries with developed infrastructures. But we can also pathogen inactivate whole blood and then we could make the components out of that.

Maybe a more practical approach for developing countries. Maybe something that we could do if we were storing whole blood in the field in military situations. So there's these two conceptual approaches that we'll hear more about during the day.

Now simple sort of scale here that we can do for many interventions. What do we gain and what do we lose by putting the intervention in place? So on the one hand, do we incur new risks? And some of those theoretical risks could be that the components that we transfuse are no longer as effective.

Or we might have acute recipient adverse reactions, or we might have chronic reactions or chronic toxicity due to expose to the pathogen inactivation agents.

On the other hand, obviously there are risks averted. And that's the reason we would do pathogen inactivation. And so clearly the transfusion transmitted infections and as a byproduct inactivation of luca sites, which could result in a protection against transfusion associated graft versus host disease.

So I want to switch gear a little bit now and talk about briefly a consensus conference that was held in Canada now 11 years ago. A pathogen inactivation making decisions about new technologies.

So many of these concepts that we'll talk about today were surfaced and discussed by a panel that consisted of a broad range of scientists, physicians in general medicine and transfusion medicine, and also members of the lay public.

And it was modeled after an NIH consensus conference. And the recommendations were written into an article by Harvey Klein and published in Transfusion in 2007.

So just to set the ground work of the kinds of debates that have already gone on, here are the PI consensus conference recommendations. Implement PI when a feasible and safe method to inactivate a broad spectrum of infectious agents is available. Why? Because active surveillance can't really accurately estimate the risk of an emerging transfusion transmitted pathogen.

Emerging agents have been detected in blood donors at an increasing rate since HIV. The reactive strategy that is find the problem through surveillance, identify it, develop a test, and then screen takes some times.

So therefore a pathogen could disseminate within the donor population before clinical disease is recognized. And the emergence of new pathogens also undermines public confidence in the blood supply.

So the intervention of pathogen inactivation could be adopted as a proactive approach in accordance with the precautionary principal. Clearly we've all heard these

recommendations if you followed the field at all and are quite familiar with them.

Now further, the group said that the same criteria should be applied to each one of the three blood components. That is safety, feasibility, and efficacy. And ideally we would have the same method that we could use for all blood components or for whole blood.

But even if we have the absence of such an integrated system for all components, it does not imply that PI for any one component should be delayed until we get an across-the-board inactivation method.

They took a look at the economic evaluations and said that of course we need to do economic evaluations. But that implementation of PI should be based on other considerations in addition to an economic analysis. And in the body of the paper, it sort of implies that the panel appeared to conclude that cost effectiveness should not be the primary driver for this technology.

And the panel endorsed the need for broad public consultation with appropriate patient and physician stakeholder groups. And I think some of that has gone on, and obviously more needs to occur. And some of it is occurring today.

So really pretty I think emphatic recommendations that PI be implemented when licensed, why do we have slow acceptance of PI, at least in the U.S. and many other countries?

Well, I've listed seven reasons here. I think they all contribute. It's hard to know which ones are the most important. So clearly we perceive the volunteer blood supply as being quite safe, so you can ask the question why do we have to do more?

And that's partially been because of the success of surveillance and screening in dealing with emerging pathogens. And clearly with the molecular testing platforms in place on some agents we're able to move very quickly. On others, we've moved really slowly, like Babesia, despite the fact that we've had that risk out

there for many many years.

Now maybe if these technologies could inactivate every single infectious organism we'd move faster. But we know that we can't. We'd miss some non-encapsulated viruses and spores. There are concerns about the efficacy of the products. No single method to treat all components. Regulatory requirements have been a hurdle in some cases. And clearly cost is also a problem.

So very briefly I think this well known to the audience. Infectious risks that can be averted by PI, bacterial leading to septic transfusion reactions for platelet transfusions, arva viruses, CMV parasites reduce the window period. And I think probably the most important, and the big unknown, is how effective this would be against agents we haven't even yet discovered.

Just a schematic here in a review article that I participated in about the effect of EIAs on total transfusion risk. So we have this baseline risk in blue. New aging gets into the

blood supply. It could be either one of these: acute agents or maybe we'll get a chronic asymptomatic infection in blood donors that we don't recognize. We haven't had one of those for a long time.

We'll get a blip in risk before we can put an intervention in. Hopefully we'll come up with a successful intervention and we'll go back down to the blue line, the base line per unit risk for all infectious agents.

Maybe increment it a little because now we have a window period transmission of a new virus. And schematically the same thing could happen for a chronic agent. The size of the peaks are just schematic. They're not real. And the length of time is also schematic.

So when we look at risks and benefits of pathogen inactivation, we need to remember something very basic. And that is when we publish on risks, infectious risks of transfusion, we do this on a per unit basis. We say one in three million units can transmit infection.

But when PI manufacturers do clinical studies, they do it in patients. And they basically say we've had 500 patients. And we had X number with a reaction. And so we have a per-patient risk. And clearly we have to normalize these so we're comparing per-patient risks or per-unit risks for both the benefits and the potential risks.

And this is illustrated for platelet transfusion in an article we published. And when we tried to -- you know most hem onc patients don't get just one platelet exposure. And so when we try to decide what the average dose was, you can see here we think it's about six apheresis platelets during the course of treatment. And you can see there is four data sources here.

And what that means is, at least if we look at the older data on undetected bacterial risk in platelet apheresis products, the studies performed around 2010-2012 with using the protection techniques that are still in place today in at least some U.S. blood banks haven't

been changed yet pending the draft FDA guidance which presumably will come out soon.

But pending that it looks like undetected bacterial, potential bacterial transmission risk is about 1 in 1,500 units. Clearly if you get six apheresis units you are exposed to that risk six times. And since approximately you can multiply by six. And so a patient has a higher per-patient risk to get a contaminated unit than they do as a per unit risk.

Same thing for red cell transfusion. It's more difficult to know the average number of red cells that a given patient gets. And clearly it's diagnosis dependent. So if you're acutely transfused for cardiac surgery or trauma, you may get three to five units. You may get B in the ICU or have cardiovascular disease.

But it you are a transplant recipient or you have a myelodysplastic syndrome or even worse, if you have Sycle cell disease or thalassemia, you're clearly going to get many, many, many more transfusions during your lifetime. And so your

risk is higher for ultimately getting a transfusion transmitted infection.

So I want to switch gears now and show a couple of slides that were in a paper that was published by Ray Goodrich who is here today and you'll hear from later. And also Brian Custer and Mike Bush.

And this is two slides, first showing the kinetics of viral infection and showing the same kind of graph that Mike had that we have low viral loads during the window period. And therefore if such a unit is transfused we would not detect such a unit. And that unit could be infectious.

And they defined a concept of PI risk reduction and a PRT window period. And essentially it's a different window. It basically says that at peak viremia you could potentially have so much virus or pathogen present that it exceeds the capacity of your pathogen reduction technology.

And so even through you might have

inactivated four or five logs of virus, if you start with eight logs of virus, there's probably enough infectious virus present to infect the recipient.

And so you may not be able to reduce risk to zero, depending on the concentrations of the pathogen. And this slide also shows something else, and that's the two dotted lines. And it shows that each pathogen reduction technology has its own performance characteristics.

So we can't, we shouldn't really generalize to PI as one thing. One manufacturer's PI system is different from another's manufacturers. And so we have to have these numbers for each system. And clearly the same thing is true for tests. We can do an HIV antibody test, but it can be first generation or fourth generation and the sensitivity will be different.

So I think that's an important point that I'd like us to remember as we go through the day and a half here.

So here's a slide about four arbovirus infections that we worried about over the last 15 years or so. A percentage of donors with symptoms, the fact that they can have severe clinical outcomes, the demonstrated transfusion transmitted infections. Yes for West Nile and Dengue. None for chick virus. Probably four for Zika, but again none of those were here in the U.S.

And the RNA screening time for the two agents that we screen for, it's been very good. West Nile virus was -- tests were developed within nine months. And Zika virus tests were developed actually within about three months of recognizing the need and implemented in Puerto Rico and then later on in the U.S.

But you have to ask the question. If we get another arbovirus infecting the blood supply, would PI be a better solution if were already in place? And we wouldn't have to worry about rapid test development.

And clearly it's going to depend, as I

mentioned on the last slide, on the robustness of the PI method and the maximal viral titer of the particular arbovirus.

So if we were to be able to put PI in place for all components, and we had every transfused unit was treated, what gains could we make? Could we drop some of the safety measures that we have in place?

And so I'm sure we'll return to talking about this during the day. We could probably modify donor testing. Of course, we'd have to get federal regulation that permitted us to do so, but theoretically we should be able to eliminate syphilis testing, CMV antibody testing, T cruzi testing and some hepatitis B testing, some of which we might be able to eliminate even without pathogen inactivation.

If it were robust enough, we could eliminate Babesia testing. I recognize that we're not all doing that yet, but we might be able to get rid of it.

For West Nile virus and Zika virus,

maybe we wouldn't have to test at all. But at least we could eliminate testing during a timeframe when the viruses were not rampant in the country.

And we probably could eliminate ID NAT altogether. And we could even use larger mini-pools. We probably could go to mini-pools much larger than six or 16.

We could eliminate or modify donor screening questions, particularly travel for malaria, which is a really difficult one because of a large number of deferrals and a large number of post-donation information reports, because of wrong history.

And we could eliminate gamma irradiation because of protection against TAGBHD.

So just to close with a few thoughts. We have seen an evolution of blood safety approaches I think. The conventional approach to blood safety has always been a combination of testing every donated unit and donor qualification and deferral.

The approach has become more flexible than it was 10 or 15 years ago. We do now have alternate testing paradigms. One time only testing as we heard for Shagas. Regional testing as we are doing for Babesia. Temporal variation as we're doing for West Nile virus, only offering ID NAT when necessary.

We have actually discontinued some tests, ALT and HIVP24 antigen. So maybe we can discontinue more when we do PI. And we certainly have put in donor eligibility questions that have come and gone for SARS when we had an epidemic, for Ebola. And so we have a little bit of flexibility that we didn't previously have.

So what's the current, direct current and future directions? Well, transfusion carries multiple infection infectious risks, but each risk in and of itself is small. So it's somewhat of a deterrent to assay development and implementation of individual agent directed safety measures because you don't get much bang for your buck.

But yet we have many things that we

could take care of it we could address multiple risks by a single intervention like PI. But the caveats are it won't work against all agents. And as I mentioned, it may not be totally effective for units with very high viral titers.

But it does change the paradigm from reactive to proactive, as I mentioned. It's consistent with the plasma fractionators approach. And it maintains trust in the blood system when a new either real or potential transfusion transmitted agent emerges.

And from that point of view it saves a lot of frantic debate and maybe premature decision making, or at least lots of research dollars being spent.

So important issues for further discussion as this meeting proceeds. Clearly the cost and reimbursement issues are important.

And now my personal view is what we're really asking. Yes we need to eliminate bacterial infection. There are other ways to do it. Yes we need to eliminate the window period, but the

effects are marginal because we don't have a lot of transmission.

So what we're really asking is, do we want to buy insurance against the potentially catastrophic event, a new pathogen entering the blood supply. I think that's what it comes down to from my point of view.

If you live in California, do you want fire insurance? Well, you might have said 10 years ago no. And today you might say yes. But you can't get it probably anymore. So do we want to buy insurance? And if we do, everybody thinks that's a good idea, to protect against a catastrophe.

And how much are we willing to pay for it? That's really the question. And it goes along with the second question. It depends. I'm willing to pay a lot if somebody else actually writes the check. But how much, or who will pay for this? How are the costs going to be absorbed? And I think we don't have an answer to that.

Second question is we do hear people

have concerns about efficacy. So what should be the efficacy requirement for a component that we treat? Should it be no change in clinical outcome, which is my preference. Or do we put a lot of emphasis on laboratory measures like CCI for platelets as an example.

And so far we've been using non-inferiority as a way of qualifying the technologies. But of course any time you use non-inferiority you have to ask how you define it and what the acceptable margin is. Another question that we could talk about.

If we do implement a new technology, what is needed to eliminate a prior method, like an infectious disease assay? And again, blood safety is a conservative field. So it's not be an inherently attractive approach to say we'll remove something. But clearly unless we're able to re-engineer our approach, we're not likely to be able to pay for everything.

And then finally, each PI technology has its own safety and efficacy profile. So each must

be evaluated separately. And I'll just close with a quote. The future, and I guess that's the question. Is the future what it used to be or are we going to embark upon a different future?

Thank you.

DR. VERDUN: Thank you Steve. That was great. Alright. Dr. Snyder is going to talk to us about pathogen reduction technologies for platelets in the U.S.

DR. SNYDER: Thank you very much. It's a pleasure to be here. Normally when I talk I talk about what we've done at Yale. I was asked to talk about what's done in the United States. So it's a little different approach. I will use some references to what we've been doing at Yale.

I think pathogen reduction is the wave of the future. I believe in the technology. And we'll see what I can do to make those statements.

So my conflict of interest. I'm doing -- I'm principal investigator for the piper study for the ceralin- based product as well as as for recipe which is the red-cell product from the same

company. I get no personal remuneration from Cerus whatsoever. All the money goes to Yale University through contracts.

The goals are to discuss what PI products are available briefly: ceralin-based, riboflavin-based, and UVC- based. Why pathogen reduction now? What are the positive and negative aspects? And to reiterate what Steve just said, why are things so slow?

When you think about it, we're still only 80 percent gluco reduced in the nation. So I can't imagine pathogen reduction is going to become 100 percent any time soon.

And what needs to be changed? Things with the FDA and other issues which we will discuss.

So this is a short paper that was done by Sue Stramer and Rich Benjamin when he was at the Red Cross. Basically just to focus on the top red bar, which is, the only FDA approved product right now is intercept from the Steris Corporation. Terumo has a riboflavin based

product. And Maco Pharma as a UVC light exposure, both of which are in phase III clinical trials.

The only approved product, however is the ceralin- based product. That's for platelets and I'm not going to go into the ones below that.

The intercept product has been used for 10 plus years. In the United States it was December 2014. I remember sitting in my kitchen when I read that the FDA had approved platelets. It was two days after they approved plasma. And I was astonished that they had done both of those so quickly. It was right, I think, the week before Christmas.

So it's been around since 2014. This is 2018. And so where are we, as far as adoption and utilization?

The riboflavin product, just for purposes of being as global as possible, the photosynthesizing agent that is used in combination with the UV light. It intercalates into the nucleic acids. It's been used in about 18 countries as of 3/15, which was a couple of

years ago. I don't have a lot of updated information.

Its CE marked and is used in various -- Europe and the Middle East. The Phase III trial called myplate is underway in the U.S. And it is not currently FDA approved.

The UVC-based product from Maco Pharma uses UVC light as the photo active agent. There is no photosynthesizing agent added to this and acts directly on nucleic acids to induce pyrimidine dimers.

And I am told, which I found out after I made this slide that there is a Phase III clinical trial coming to conclusion in Germany. And the company expects to have data available by the end of 2019. So that is further along than this slide would imply.

So I asked myself how many publications are there in pathogen reduction. And here, by searching Pub Med -- actually I didn't search it. I ask Wade to search it and he did it about five nanoseconds, which was scary.

Searched by pathogen reduction, pathogen and activation, blood, red blood cell platelets and plasma, done on 11/18. So as you can see there is a fair number of publications up to about 70 or so per year now. I would have thought that might have been higher, but I would expect that the slope of that will be positive.

So Yale, just to give you an idea when I do talk a little bit about Yale, we're about 1,600 bed, about 10,000 patients, about 45,000 blood products. And as you can see we have changed our platelet usage.

We used to use a fair amount of the pooled-random donor. Since that's not approved for pathogen reduction and we've committed to go to 100 percent, we have only about 600. This was as of the end of this one. I'll show you the slide. And about 9,400 units.

So we've transfused about 10,000 units of platelets a year at the institution. And we've had a large influx of oncologists, primarily from Johns Hopkins I believe. And they were looking

for single donors. And they were -- we have increased our cancer center activities dramatically, which I think has an impact on what you will see.

The question is why now? At Yale, and I think it's for the country. And Steve alluded to this. Why are we doing this? Because safety measure does not cover viral or other nonbacterial pathogens. End of story. That's why we did it.

We went to pathogen reduction because I don't want to have worry about the next virus that jumps out of the jungle in a foreign country and gets into the humans and into the blood supply.

Large volume, multiday bacterial cultures, and all those letters are just basically what the above line says, does not cover viral or other nonbacterial pathogens. I could not see us spending millions of dollars to establish a bacterial detection system only to have a virus come along that would be, you know -- why did you spend all this money, Ed, if you're not dealing with a virus. You told us everything was going to

be fine.

And the infrastructure is not feasible, as I mentioned. The capital costs and the IT challenges. Some places have done it, and they've done it well, and it's wonderful, and you hear from some of the people who talk about this being beneficial. It doesn't do anything against the viruses and the unknown pathogens that are coming.

Over the past 18 months at Yale we have had five septic transfusion reactions. So it's not like, yeah well it doesn't happen here, because it did. And we had two donors who were responsible for five reactions.

And why? Because splits. One pathogen-reduced product was divided into three. Another was divided into two. And we got five. And that caught the attention of our administration. And I will explain that.

This is the classical contaminated platelet. This actually was my slide I found on the internet, the classical EDS is not my slide. It's not Ed's. It's egg drop soup, which I do not

eat anymore. I'm going over to hot and sour.

It was reproduced with someone's permission, but it wasn't mine in 2004. And I know its Yale because we're in the lower right-hand corner, has the Yale logo there.

So like many places, everything is sports paradigms these days. We had a technologist who saw a unit that looked that. She introduced it. It was staphorous. And she got -- and it was a triple.

So three people did not get that product. One was outside of the institutions. So she got the good catch award, which she did have to give back. She only kept it for a month and then someone else gets it.

But we had problems with Staph epi and Staph aureus. And we thought that, well those are pretty standard. And then a couple of other organisms came along I had never heard of. There was strep bovis, now known as strep galloyticus, and the ever popular (inaudible), along with staff saprophyticus.

At Yale, we have decided -- they have decided, to their credit, that this Venn diagram is congruent, that patient safety and dollars both have equal weight. So the institution was willing to give us the additional cost that it took to convert the blood -- the platelet supply to 100 percent pathogen reduction.

Not every place has that luxury, the ability to do that, or the will to do it. But Yale has done that. So safety eclipses cost at least at our institution, as it is as many institutions. You just have different ways of trying to figure out which pathogens you want to go after.

The label copy allowed us to use this product for everyone, so nationally you can use this product for neonates, for pregnant mothers, all the people listed on the left side over here. Jehovah Witnesses obviously it's not acceptable unless their religious beliefs permit that.

And I'll talk about this fake new, I guess, because there's another issue there.

Okay. So this is an important slide. The more I look at it, the more important it becomes to me. What you see here is pathogen reduction use at Yale New Haven starting October 2016 going to October 2018. I couldn't get the November stuff because we're still in November.

So the green is the total number of platelets used per month at Yale. The blue is the non-pathogen reduce or conventional, which at that time was the PL5, which is the pooled random donor and single donor not pathogen reduced. And the red is the pathogen reduced.

So why is this important? Because right over here in September there is an inflection point which I believe was the ABB or around that time when the guard bands started to get -- and the Red Cross is our primary provider, along with the Rhode Island Blood Center.

The ability to deal with the guard bands became a little better. And so we had a bump up. And then we sort of continued along. And then around February the Rhode Island Blood Center got

their BLA, biological license application. So the amount increased.

So people looked at this. And some people said well sure. The more platelets that are pathogen reduced, the more platelets you are using. So the pathogen used platelets aren't working, because you're needing more of them.

Well, when you look over here, from September '17 through February '18, there's an increase of the amount of -- total platelets has not gone up. If the platelets weren't working and they were asking for more platelets, I would have expected that there would be a rise in the total platelet use and the blue would go up because we would need more platelets and we couldn't get any more pathogen reduced.

And as you can see here, we're down to about 100 a month now. And all of those pathogen -- all of the products that have been contaminated have been in that miserable five percent that we can't get rid of yet that is causing all of our infections, as we'll talk about in a couple of

seconds.

So when I look at this slide, it gives me general information that the pathogen reduced product is effective hemostatically and we're not using more platelets because they are bleeding or the CCIs are so low that the physicians are requesting more platelets. Again, this is just a general gestalt from this.

So how did we cope with this obvious dual inventory? Well, we started off by just saying well just go with pathogen reduction. That raised a whole bunch of issues which will be viewed nationally.

So I decided that pathogen reduction was conventional plus a safety measure on day five. And I thought that was pretty cool. We had the whole thing. We're not required to do it. Except along came strep bovis or strep gallolyticus, which was a contaminated product on day four.

This is seen with patients with colon cancer. Our blood supplier checked with the donor. The donor did not have -- had a

colonoscopy actually and was found to have had a strong history of diverticulitis, diverticulosis makes quite a good deal of sense. This may have been the source of it.

But here was at day four that was contaminated. We had three sick patients. So now the paradigm was PR = CP + SM4, 5. And I thought that's it. All done.

Then along came Acinetobacter baumannii, which was not detected by the safety measure, along with strep saprophyticus, which apparently goes along for the ride.

And the institution looked at me and said well, we spend all this money and you're still getting infections with this five percent. These are all non-pathogen reduced products.

So what I decided to do was add GS, was a gram stain. So now for every conventional product that's day four, day five, when permitted. We're not getting something at 3:00 in the morning as an emergency. We'll do a gram stain. Why?

Because I want to see if the product is

so totally contaminated that it is potentially lethal, which those other products were. And if there are a few bugs, but the gram stain is negative, I have to go with that. What else can I do? There isn't much else that one can do, except get 100 percent pathogen reduction.

Then I thought well I'll just pour bleach in each bag. Why not? But then I look at the bleach and it only kills 99.9 percent. That's only three logs. That's not good either. So I don't have any good answers. We need 100 percent pathogen reduction. And bleach isn't going to work.

I was very surprised at that, but there you go. So the adoption evidence that we reviewed, which all institutions around the country will need to look at is, when my plate and the theraflex as well as intercept.

We looked at what data there was. And with multiple experiences, multimple studies, multiple populations, it wasn't just one study done by one individual in a van down by the river.

There was a large period of time where these studies were being done in Europe, while the FDA was deciding whether to pathogen -- approve pathogen reduction in the United States.

So we felt that this was a robust product and was able to convince the institution that we needed to do this. And obviously there's ongoing human vigilance.

There is data that has been reported from other countries. This slide I think summarizes it quite nicely. This is an updated slide. And I got this from the Cerus Corporation because I don't have access to this data.

For a total of three million produces since, I guess, 2012 in three countries, there were 76 -- this is conventional platelets in blue. There were 76 cases of sepsis with 12 fatalities. About 25 percent intercept products given in those countries and no sepsis or fatalities.

Promising? It's only 25 percent of the total. But the data is continuing to accumulate. So we took comfort in the fact that this actually

is working and is being used in these countries for a while.

The major benefits of pathogen reduced platelets, be they riboflavin or sortilin is that it affects the bacteria lipid on both viruses, protozoal emerging pathogens. It also eliminates the need to do gamma radiation because it's more efficient that gamma or x-ray.

I have gotten multiple calls from institutions where oncologists have not wanted to adopt PR because they say it's going to cause graft versus host. Apparently it is not. That is not a requirement. And you don't want to do both because both of them will have a negative effect on the platelet function.

Gamma radiation and pathogen reduction. So that's not appropriate to do that. But that's something else people are concerned about. Decreases cytokine generation and allergic reactions because if it's in the amicus collective product they remove about 65 ml or so to put the path C in. If it's entreama, it's an otologist

plasma. So there wouldn't be -- wouldn't come into play.

So there are multiple benefits from pathogen reduced products viewed from our institution. There are some constraints. As I mentioned, the amicus requires only five days in PATH C, trema only autologous of five days. There's no seven-day approval.

It's only limited to doubles and singles. There's no triple, which is about 30 percent. Which means that the supply side is impacted negatively. Why? Because you didn't submit the data. So the FDA didn't approve anything if they don't have the data to evaluate.

Guard band requirements are a concern. BLAs are taking a long time, 12-18 months, to get approved. And that means you can take approved product and you can treat anyone in your state, but you can't cross a state line and give it to someone else. That's a potential concern. And that has also limited our ability to get additional product. And I'll go into that very

briefly.

So I got some of these slides from the Red Cross because I don't have access to national, but the routine pathogen reduction was initiated by the Red Cross. And that's the only blood center I can really discuss.

In July about 13 manufacturing sites have implemented intercept and are producing it to about 50 customer hospitals. We're over here in Farmington. And that's really -- there are other blood centers that are doing this. I think NIH is manufacturing their own.

So that's kind of where we are. Licensure. Red Cross anticipates receiving a BLA for Baltimore by the end of the year and anticipates getting optimization of the SOPs and working toward the other sites under the CBE changes being affected approach to the remaining sites by the middle of 2019.

So it's ramping up. It's a little slowly, but the snowball is rolling more quickly down the hill.

The limitations. Again, the lack of FDA approval for many variations on platelet themes. The extension of time for the approval. And also the concept which is really quite something. It has to be remembered.

Once the illumination in the little Easy Bake Oven shuts off, a pathogen reduced product is vulnerable to be contaminated. So if you have a leak in the bag or you have a micro tear or whatever, and organisms get in there, it is as if it wasn't an activated at all. So you can't just, well it's been activated so now its Teflon coated and you can do whatever.

That's a concern. Post-breaches in the closed system bag is a concern, which we don't talk about very often, but it has to be considered.

And the inability to treat all platelet products. And I think one other reason for lack of implementation is the lack of robust data on pediatric neonates and pregnant women, which I'll get back to in a second.

So the difficulties in the guard banks was a supply side problem. Cost is a problem for all institutions. There are concerns about the lower post-transfusion CCIs and lower hemostatic efficacy. CCIs may be lower, but it's not associated necessarily with an increase in platelet use, which means physicians tend to over transfuse platelets.

We've published some data. I'm not going to go into that. This is not a data dense type of a presentation. But we've had several presentations on adults and neonates at the ABB. Also at ASPHO, the American Society for Pediatric Hematology Oncology. We presented our Yale data. Nothing to do with piper. It was the data from our institution.

And the risk of TAGVHD we don't believe is a concern, but other institutions do. And also the time to implement. It can take 6-12 months before the institution will be able to adopt it.

This slide was originally from Jim Obeshon showing that the gamma radiation has one

in 37,000 base pairs and amotosalen has much more.

The slow adoption. When she stands up it's a bad sign. It's a very bad sign. Concern over skin rashes was a concern for platelets in neonates. And we took a look at that. You are all aware that the absorption is low, 375 is a concern. The ones that are used in the U.S. are well above that.

And we evaluated it and we found for those individuals, conventional you wouldn't worry about it. For pathogen reduced neonates, neonates would receive pathogen reduced platelets. There were 11 who also received the blue light therapy. And there was no evidence of rash, nor should there have been.

But we just wanted to document it. And that's also in the manuscripts that we have submitted.

These are the transfusion reactions. Are there an increase in transfusion reactions? We found only an increase in septic reactions in the non-pathogen reduced conventional products of

which there are about 8,000 conventional, 8,000 pathogen reduced from 2016 to 2018 which was significant. So the answer there is go to pathogen reduced, which we're trying to. But the bugs will not let us.

There are concerns about long-term toxicities from repeated administration of psoralen in infants and neonates. I thought there would be much more data coming out of Europe, but there isn't.

Psoralen. There is lots of psoralens in food. Celeriac has a large amount, 70 milligrams, which is celery root. And it makes a lovely salad, which is -- if you can get through it, no organism will harm you for about two days.

There are studies which I'm not going to go into because Simone is standing there showing the compound absorptive device will remove photo products. As you can see the important thing is that the bottom line here is close to being flat.

This is a standard. So it's removed pretty much. You're talking Nano gram or

pictogram quantities when Celeriac is milligrams, but you know they are not exactly the same. Amatocilyn is a synthetic product. So they're not exactly the same, but there is some toxicologic data also on neo-antigen formation which I won't go into.

Riboflavin, similar evaluations. So no new compounds formed. Everyone is looking at toxicity. But the concern about -- what about the toxicity of the bacterial infections that almost killed five patients at Yale? I mean there's -- there's no free lunch anywhere.

So the slow adoption. I think we've gone over this. The blood bourn threats are regional. Some concerns about the ethics of managing a dual inventory. That's why we have the equivalence.

I didn't want to have to decide who got what product. We consider them equivalent. But we're trying to get 100 percent pathogen reduction as quickly as we can.

Cost is a big concern. Cost I think is

a major concern, but people are saying, well what about toxicity? The platelets don't work as well. Your CCIs aren't as good. I think the data nationally shows that these are still concerns and they are valid. And they have to be looked at.

The FDA guidance. I think you are quite aware of that already. The reactive approach where an organism is seen and as Mike and Steve talked about, you then develop a whole system to identify it and get a test for it. Who is going to buy it? Who is going to pay for it?

If you have a proactive approach, it's already there waiting and ready to take care of it, assuming it's a susceptible pathogen, which generally it would be. Whether it's riboflavin-based or ceralin-based or potentially UVC.

So also I think a very important thing is in the bottom here. Do not underestimate the ramp-up time when something happens. It's going to take a very long time to get this on board.

And the hospital experience to date is

several large academic centers have converted. People are concerned about the issues that I talked about. The delayed guidance, the -- a lot of hospital aren't aware of the other mitigation strategies that are there.

So what is the status in 2018? According to the company Cerus, there's about five million products that have been given out since 2002. It's available at 200 centers in 30 countries. The U.S. hospitals use insulin-based products. There are about 130.

There's a lot more hospitals than 130 in the country. So it's about ten percent of the Red Cross's single donor products are pathogen reduced. And nationally it's about seven to eight percent of the total platelet supply, as I understand it.

And it does take a village, if you want to implement this. This was our village which was everybody under the sun, including people who didn't have any contact with the platelets, but everyone needed to buy into it. It was a year-

long process.

What about CMS? CMS was paying $641 for 2016. Then they lowered it, or threatened to lower it, were considering lowering it at the beginning of -- the end of this year for next year. But then they got responses from the community. And now it's back up to close to where it was at $623 for outpatient. Inpatients under the DRG.

So what are the factors? Early implementations were constrained by capacity and availability. You need product requirements, further limited production. You couldn't give a lot of -- if you want to give an HLA-matched platelet, the chances are it's not going to be pathogen reduced because you can't -- you'd have to select a donor and then pathogen reduce that product.

So that's -- I think dual inventory is here for a good long time.

Uncertainty regarding the guidance. Precocity of data. The anticipated and ramp-up

time and the cost is a concern. And again to quote Alexander Pope, that my mother used to do that you're not the first by whom the newest tried or the last to lay the old aside.

So we're very far ahead of the curve. I realize that. What's needed is publications and data for the United States to increase above the 130 hospitals. And it's coming but it's going to be a slow process as I see it.

Thank you.

DR. VERDUN: Thank you Ed. That was great. So Dr. Aubochon is going to talk to us about pathogen reduction technologies for plasma.

DR. AUBUCHON: Thank you very much. I was looking forward to Steve's presentation in my slides, but apparently I will have to give the presentation. I do also appreciate the invitation to have learned more about various forms of pathogen-reduced plasma. And I look forward to sharing my observations with you.

Thank you. I have no conflicts of interest in this matter, at least over the last

decade to report. I agree with Steve on the comments about terminology. And I recognize that's not the agency's preferred terms.

However, I will try to adhere to the same approach of distinguishing pathogen and activation as a technique in the final blood components, which are pathogen reduced.

I will be discussing this morning data from three different forms of pathogen-reduced plasma two of which are licensed in the United States and one of which is not yet, but I anticipate it is not that far away.

I won't be talking about Methylene Blue - or UVC- eradiated plasma as these are not approved in the United States and do not appear to be approaching imminent approval.

I'll just make a quick comment at the beginning that many hospitals have come to enjoy the availability of plasma, which has been previously though, either prospectively or just thought and not used and then stored in the liquid state for utilization at a later time.

Neither of the two licensed solvent detergent or intercept plasma approaches can be converted to thawed plasma and have to be used relatively quickly after thawing. Hopefully this will be able to be changed in the future.

There are many papers on the literature which note the effects of the pathogen inactivation process on the content of various proteins in the plasma. And I'm not going to show all of them here, but one format that one often sees is a pre-treatment versus a post-treatment concentration or activity.

And some of the proteins in plasma certainly do seem to have a reduction in their activity as a result of the treatment. However as it has been pointed out, the reference range for the content or activity of these proteins in any one individual donor's plasma is quite large.

And uniformly the reductions that are seen from pathogen inactivation do not cause a greater change than one might see in the normal donor-to-donor variability.

The contents of different papers are very different, but the contents of their data appear to be quite similar. I found only one paper that looked at compliment factors, treatment with intercept. And there didn't appear to be any great differences there.

In mirasol there have been two papers published. And I show the data here as percent reduction. I'm sorry. Percent retention. There are certainly some components that are plasma that are more affected, as I will summarize in a couple of slides ahead. Particularly Fibrinogen is noted, (inaudible) for mirasol factor XI as well. Although I don't know exactly what clinical impact that would have unless were factor 11 deficient.

The content of fibrinogen and factor VIII seem to be most likely to be reduced as a result of any of these pathogen inactivation treatments shown here, but as percent retention or the actual concentration. And you can see that any of these techniques to a slight reduction.

Again, more data. You can spend weeks

looking at all of these data. But again, they show for fibrinogen and factor VIII in particular some reduction shown here as a nice comparison with different techniques. The untreated being the black bar.

And all of the techniques seem to have about a 20 percent reduction of fibrinogen which occurs and a factor VIII a little bit more than that. The largest reduction there being in factor VIII.

So here is my compilation of content reductions that are 20 percent or greater. This is not a quantitative meta- analysis. This is just my view across the published literature. And you can see there which of the factors seems to be reduced, most frequently reported with any of these techniques.

Of course the solvent detergent technique, Octaplas, in its original formulation is shown to have productions of protein S and C and was associated in high volume usage, particular in liver transplantation with

unexpected thrombotic events.

In the current formulation, which is a different process that does not appear to be a clinical problem as I will show in a few slides, but there is still some reduction in protein S.

There is content variability in every unit of FFP because of the variability in the donor's arm that we cannot control. And in a pool technique such as solvent detergent plasma, the range of variability can be greatly reduced. That is a plus.

One does have to consider, however, that each of these units, although they are very similar when you are looking at a pooled product of solvent detergent plasma, they are smaller units. So you have to consider not only the size of the unit and also the content of the plasma.

There's an interesting paper suggesting that with mirasol treatment, there may be the potential for reducing the reduction, or preserving the retention of certain factors including adams XIII and fibrinogen and factors

VIII if the technique is conducted in a low O2, or that is mostly an aerobic environment.

I haven't seen other papers on this. Interesting concept. And we'll have to see if this is evaluated further by the manufacturers to improve their techniques.

What about making Cryoprecipitate from plasma that has been treated? And it does appear that one has to get past the reduction and factor VIII and fibrinogen which is in the plasma but then Cryoprecipitate can be prepared with a normal distribution of (inaudible). The same can be said for mirasol cryoprecipitate as well.

So the amount of these important components, particular fibrinogen and cryoprecipitate will be reduced, but still a useable level can be maintained.

Intercept plasma has been reported to be used in a number of different situations, including those patients who are congenitally deficient in different coagulation proteins. The number of patients and number of transfusions

reported has been relatively small. But the recovery is approximately what would be expected.

Because these are patients. Because the number of transfusions is small the percentage of recovery may appear to be lower than the reference values. But have all been reported to be useful in a clinical sense. So the patients did well and had a normal hemostasis that would be expected after infusion of intercept plasma.

Intercept plasma has been used in large volume exchanges in a number of different clinical situations. In ITP, for example, there were no difference in outcomes using the intercept plasma or in the adverse events that were reported.

In plasma exchange, having IM plasma exchange for TTP treatment. Again, there was no difference in outcome for these patients. They did well and they maintained adequate clinical hemostasis throughout these plasma exchange procedures.

Here is another large volume exchange series reported. Which again there were no

statistically increased incidence of adverse events.

Using intercept plasma in liver transplantation appears to be effective. There was an increase of the number of red cell components that were transfused as well as platelet components that were transfused in the intercept plasma arm of the study.

However, it was also noted that those patients appear to be slightly sicker at transplant and had a longer transplant delay time. So this may have factored into the likelihood of needing more transfusion support during the time of transfusion.

The authors felt that intercept plasma yielded the appropriate clinical outcomes that they were looking for. And they did not see any evidence of either hyperfibrinolysis or thromboembolism in the patients that they studied for that, that received intercept plasma.

There have been a number of studies in vitro looking at the ability of PRT plasma to form

clots. In general, the clot is not exactly the same as one sees in untreated plasma, with thinner fibers, slightly denser clots, and decreased clot permeability.

With mirasol plasma there is slightly greater lag time in formation. With intercept plasma a slightly prolonged time to licsus.

So does this make any difference clinically? And indeed this was taken to the point of asking the question whether using PRT plasma in massive transfusion situations would lead to increased patient mortality.

The think that with this decrement of activity in multiple different plasma constituents might then reduce the amount of effective plasma given. And it was noted that in the proper trial, better outcome was seen in the first time period with a 1:1:1, then a 1:1:2 ratio and therefore using PRT plasma might essentially the ratio from what the trauma surgeon was thinking that he or she was using.

However rebuttal was promptly submitted

noting that the two arms of the proper trial had equivalent survival at 30 days and that the activities post treatment with intercept plasma in particular are within the range of standard frozen plasma as I noted and that most commonly a goal-directed therapy approach is used.

And that is, although the components are prepared and initially transfused in a standardized format, most institutions will then follow up to make sure that the patient has achieved the goal that was predetermined or was expected. And if not additional product would be given.

So those are the two theoretical issues to be addressed here. What about actual information?

In vitro constitution using functional assays as the endpoint with a 1:1:1 combination volume showed that at a 30 percent blood replacement, there was no effect of using treated plasma. At a 50 percent blood replacement, there were some changes evident. But question really

those changes were of any clinical import.

And indeed studies reporting the effect of using intercept plasma in massive transfusion patients documented that there was no increase, in fact possibly even a slight decrease in mortality associated with intercept use, and no difference in the number of other blood components that have to be transfused along with that plasma.

Therefore, at least in this study, they felt that intercept plasma was entirely appropriate to be used for massive transfusion situations.

We're all aware that plasma usage has many risks, a number of different kinds of reactions which can occur. And is there any benefit of using pathogen reduced plasma to reduce those risks?

Although the major risks are quite low, if you multiply those risks by the number of patients receiving plasma or the number of units of plasma transfused every year in this country, those are significant risks to consider.

In one study it was noted that there was no statistical difference in the use of intercept plasma in causing adverse events of severity grades two, three, or four. And the reactions that were seen were all of the allergic type.

Meta-analysis has been completed looking at the reaction rates using frozen plasma, intercept, or Methylene Blue, or solvent detergent plasma. And I recommend this article for your review if you want to look at the details.

In summary, there was slightly lower fibril reaction rate with Methylene Blue. The male only TRALI risk. The male only plasma TRALI risk was about the same as for solvent detergent plasma, which was less than the mixed-sex frozen plasma TRALI list. But there was a lot of heterogen (inaudible) between the studies. There is certainly an argument that the dilution of the antibodies in plasma that may be present in plasma during the solvent detergent pooling and processing would reduce the TRALI risk. And indeed there have been no reported cases of TRALI

after transfusion of 10 million units of plasma in Europe. So this looks very comforting.

And indeed one study noted that if the TRALI risk of untreated plasma was 1 in 5,000 or greater, then solvent detergent plasma became cost effective. Although I would point out that even a minute risk of severe non-envelope viral risk occurring in the plasma supply would negate all viral protection benefits.

It's not something that we are greatly concerned of today. And most severe human pathogens are lipid enveloped and would be treated by a solvent detergent plasma. But this is at least a theoretical risk.

Now, I appreciate that the FDA has long regarded as transfusion safety like an onion. I like onions, so this works well. And there are many different layers to that. And indeed pathogen inactivation would appear to be an important additional layer as others have pointed out.

How effective are these treatments?

These treatments all have high probabilities of reducing the infectivity of viruses below any level that we would generally be concerned about. And these reductions, of course, are not necessarily limited -- not showing the limits of the technique, but sometimes they are just showing the limits of the assay system. And so actually the effectiveness may be greater than what is seen here.

With solvent detergent treatment, one does have to worry about non-envelope viruses because the technique does not affect them. But there are other testing techniques that are used to reduce, if not essentially eliminate, the risk for example of parvo virus and hepatitis E virus.

Interesting, solvent detergent plasmas licensed in this country is produced from source plasma. That is paid donors. And when this first became available, I talked with some of the hospitals that we served asking their interest in solvent detergent plasma and whether this was a major concern.

And interestingly none of them were at all concerned that these were paid donors, which surprised me. But they are ultimately the customers. However when we got to talk about how much it cost, then their interested waned rapidly. And we can get back to that.

Intercept is similarly effective across a wide range of model viruses and other pathogens as well. Mirasol numerically appears to be slightly less effective, but again for the -- adding this onto the techniques we are currently using in the testing laboratories, certainly more than adequate.

So as we've looked at the evolution of plasma transfusion risks over the years, when we began thinking about pathogen inactivation as an approach, we had the lay media frequently noting that we were losing the battle with respect to keeping the blood supply safe.

That was then. This is now. And so why would we not be concerned about pathogen reduced plasma. Others have noted the risks of emerging

pathogens. And we're all aware that it's only a short plane ride from a chicken market in Asia to the United States and possibly introducing, by this means or some other, a new pathogen into our blood supply, including the plasma supply.

The consensus conference that Steve mentioned did note that a reactive strategy should be supplanted by a proactive strategy and that we should move on implementing pathogen reduction approaches even if we don't have it available for all components.

So in my estimation, pathogen reduced plasma is safe. And it is effective. The question really comes down to cost. And I'm sure that we'll hear later today from Brian Custer about the issue of pathogen cost effectiveness.

Pathogen inactivation cost effectiveness plasma has a role in that certainly, even though possibly less an impact than with red cells or with platelets. And indeed pathogen inactivation can reduce cost in certain scenarios.

The ethics of all this we haven't really

addressed yet today. And there is one paper recently in the literature talking about what should patients be told about pathogen inactivation and other safety measures in transfusion.

The question is what would patients want? If we asked them, what kind of plasma would you like to receive?

What have other done? I would like to show you a map of the United States showing implementation of pathogen reduced plasma, but there would be nothing to show. Very little use of plasma that has been pathogen inactivated is occurring in this country.

With the help of some friends I was able to gather information from Europe where these techniques are more commonly utilized, particularly in North Europe. Solvent detergent plasma is pretty much the only form of plasma that is available.

And then you get to the rest of Europe and it's more viable approach, some using either

multiple techniques, solvent detergent and intercept and mirasol, and others still using quarantine plasma to some substantial proportion of their plasma supply.

So I can offer my conclusions and observations and a few predictions that although pathogen reduced plasma is safe and effective, despite some activity content reductions, there may addition a reduction of some noninfectious adverse event risks that may be attractive.

But given the current level of safety of plasma, where bacterial contamination is not a concern, as it is in platelets, there really is little impetus to adopt a pathogen introduced plasma in the United States at this time even though there is a very clearly worded consensus conference statement that we should be doing so.

And I think we will not see widespread adoption of pathogen introduced plasma in the United States until we have a system available for all blood components and possibly also unless the FDA mandates its use.

Because the most common comment I hear from introducing safety measures to hospitals is well, when the FDA says we have to do it, then we will pay for it. But not until.

So if someone says it's not about cost, it's about cost.

Thank you very much.

DR. VERDUN: So I'm going to be collecting questions if there are any from the audience or online. Steve do you know if there is anything? Not yet. Well I prepared a few questions.

So the first question to the panel in general is that the consensus conference said that we needed to have broad public consultation. So how has that been done? How have you engaged patient and physician stakeholders to get their opinion is on pathogen reduced products? Anyone wants to take that one?

DR. AUBUCHON: I can offer that in our region of the Pacific Northwest, forgotten corner of the country, is that we have approached our

hospitals through various advisory committees that we have on several occasions offering them information about pathogen reduced plasma and platelets and the status of the development of red cell systems as well to keep them informed and to gage their interest.

I have not seen resistance to the utilization of these components or concerns about their safety. The concerns about reduced effectiveness are obviously always of potential concern. But we've been able to produce data from the literature to show that the patients would do as well.

And those have been accepted. It always comes down to the cost. They say, well how much more is this going to cost? And when we get pushed back about adding a few dollars for a new test, you can imagine what happens when we're talking about increasing the cost of a component by 20-30-40-Percent or in some cases even doubling the cost of a component.

And the hospitals baulk right there and

say, well we're not interested in that. So I'm afraid that at least at the consumer end, if you consider hospitals as our consumers, we are unable to convince them of the necessity of moving to a safer blood supply.

I would add very unfortunately.

DR. KLEINMAN: I don't have an answer, but just an observation that I know there's been a lot of stakeholder consultation in Canada. And we have Dr. Devine here from Canadian Blood Services who could maybe address that, if that would be of interest.

DR. VERDUN: Yes. That would be great. Thank you Dan.

DR. DEVINE: Sure. Thanks Steve for the Canadian prompt. We have been undertaking quite a bit of work to get stakeholder opinion. And we have mechanisms for doing that.

Some of it has been done in very formal surveying of physicians who would potentially use the product. And there was a study lead by Nancy Hettle at McMaster who will be known to most in

this room. And she really tried to get a sense of what the interest in the community would be of using these products.

We have continued to do that sort of surveying through national groups that we interact with on a regular basis for understanding how to make policy changes in the blood supply in Canada at the physician level.

And then we have an equivalent process for getting stakeholder input from recipient groups. So in Canada we have a lot of very well organized patient advocacy groups of people who received blood and blood products.

And so we have kind of a natural way to get that kind of opinion piece. And so we do have the opportunity to get lots of input.

DR. VERDUN: Thank you Dana. Ed, do you want to --

DR. SNYDER: Yeah. At Yale I like, like other places, if you want to have pathogen reduction technology imported into the institution, there needs to be a champion in the

institution who is going to notify the administration that this is an issue that needs to be addressed.

I've used the have need phrase. You either know your jewels or know your jeweler. If I go and talk to them and tell them that we need to have pathogen reduction, they will listen.

You have to put it into administrative readable form. So you don't go and say we need it because we need to save lives. You go with a business plan. You go with a PNL statement. You show them that you are as concerned about the economic impact on the institution, because there is not right now a credible threat.

The fact that we've had five septic reactions, this occurred after we had already convinced them to start with the pathogen reduction. And for our institution, it was a couple of million dollars additional cost.

But they felt that there really was a requirement to ensure safety of our patients and things could theoretically be a lot worse. Once

Yale moves, as they say in Connecticut, as Yale goes, so goes the state.

So the rest of the state started to pick up. And as the hospital grows in its catch mineria, more and more hospitals get pulled into that.

So it again has to start with an individual who goes and pushes for it. It's not just going to fall out of the sky without some credible threat that's in the papers every day.

So it does take someone who believes in the product to push it forward. And I think that's true across the country.

DR. VERDUN: Thank you. Anyone has a question?

MR. BENJAMIN: Richard Benjamin, Cerus Corporation. I just wanted to add something for clarification to a comment that Dr. Busch said about thawed plasma. Cerus realizes that thawed plasma is an issue with intercept plasma.

And there has been a formal request to the AABB, I believe it was from the Navy to allow

thawed plasma, because that's not an FDA product. It's an AABB. And they have, I understand, accepted the idea that intercept plasma could be converted to thawed plasma.

And we have actually on the advice of the FDA been asked to remove the 24-hour requirement from our packing cert. And we are in the process of doing that.

So we do believe that when that is done you will be able to convert intercept plasma into thawed plasma with a five-day outtake.

DR. KLEINMAN: I just want to make -- something that has always perplexed me about plasma is the difference between the European and U.S. regulations. And as I understand it, this is not relevant to thawed plasma, but plasma safety in general.

As I understand it, at least in many European countries you cannot transfuse a unit of FFP without having done something to it. So you can quarantine it for six months and get the donor back in order to prevent a window period

infection.

Or you can treat it with an approved pathogen reduced technology. But you cannot take it off the shelf and transfuse it. And it has always dismayed me really that in the U.S. FDA has accepted the risks for transfused plasma whereas the European regulars have not.

So I don't really know if I expect an answer to this, but I think it's worth hearing.

MR. BENJAMIN: Steve, I don't have an answer to you. But one comment is that for the longest time England was important plasma from the U.S. for their pediatric patients. And Methylene Blue treating it before they gave it to their patients.

So that clearly is a comment on their opinion of the U.S. plasma supply.

MR. BUSCH: Point to that issue is that if you -- I didn't get into the details, but if you compile all of the breakthrough transmissions of HIV and many other viruses, plasma is by far our riskiest product. The volume of plasma that

is transfused and most of the agents were concerned about are in plasma.

So there is a number of cases where plasma transmitted where corresponding red cells or platelets did not. So the ability to inactivate plasma I think makes a ton of sense.

DR. VERDUN: Thank you. I had a question on the platelets products risk benefit ratio. Does it matter when -- do you think about this ratio differently depending on whether it's therapeutic versus a prophylactic use for platelets?

DR. SNYDER: I'm not sure I understand that complete. Are you willing to take more risks if it's a therapeutic as opposed to a prophylactic?

DR. VERDUN: Right.

DR. SNYDER: That's a tough question to answer. I would think in a sense, you know, if we need platelets at 3:00 in the morning because there's a patient who needs it and all our supplier can give us is a non-pathogen reduced

unit that's four days old and we don't have time to so a safety measure or the other things I talked about, we'll give it.

We try to convince physicians to realize that giving a blood product at any time, we all do, is dangerous. And you have to be able to justify it if something untoward were to happen.

So in that sense, I guess yes. If it was a prophylactic transfusion, we would ask them to wait until we finished all of the testing. If it was therapeutic, we would use it, you know, without doing it if they realized that it needed to be done and could justify it.

So I guess the answer is yeah. We do have two different levels if we're forced to.

DR. VERDUN: Thank you.

SPEAKER: There was only slide this morning showing the effect on the T cell and T cell inactivation or the cell inactivation by these technologies. And I'm wondering what the opinion of the panel is to the effect of preventing confusion associated graph versus host

reaction.

That's a big thing I think once we get to 100 percent inactivation including the red cells because then all patients would benefit from this preventive measure which has nothing to do with infectious diseases obviously.

But perhaps a lot with immunologic effects in the recipients.

DR. KLEINMAN: So I just myself, along with a colleague who used to be at Cerus, Dr. Stasonopolis, just published a paper in the November issue of Transfusion. The general view of transfusion associated graph versus host disease along with some newer in vitro data limited T cell cloneage, limiting delusion assay data, with the Cerus product.

And it's clear that the degree of T cell inactivation accomplished by intercept treatment is at least as much, and actually more, by these new experiments than the degree achieved by gamma radiation.

So that's one point. There are also

experiments with the red cell technique that -- and the platelet technique has been pub -- the platelet data has been published in an independent article in 2017, I think.

The red cell data is new. We summarized it. It's not yet really been published in detail. And the second factor here is at least through human vigilance systems, there has been to TAGVHD from intercept-treated platelets in Europe, in the European countries.

So I do think that the data is fairly compelling that you're going -- and there is a lot of in vitro data as well with that formation, et cetera being better.

So I think the data is very compelling that you get at least equivalent protection against TAGVHD, if not better. And I'm surprised that clinicians are still concerned about it.

But I guess the basic thing is nobody sees TAGVHD anymore. So they say, well we have a perfect intervention. Why would we want to take a chance and try something else?

So it's pretty hard to kind of introduce a new technology for that same indication when the current technology seems to be effective.

MR. BUSCH: I think beyond TAGVHD, I mean, lymphysites in products. And of course most of the pathogen reduction is being on already (inaudible)-reduced. So I think there is interest in potentially eliminating (inaudible) reduction.

But there was quite a bit of hope in research done by colleagues of my institution: Philip Norris, Rachel Owen, and Rachel Jackman on the ability of these inactivation technologies, both the Cerus and Turomo to reduce antigen stimulation and potentially prevent alloimmunization.

And although in vitro there is definitely large effect of these treatments on antigen presentation and immunologic stimulation of recipient cells, if you actually do studies prospectively and this trial and the preparers, there was not a significant reduction in alloimmunization rates in the pathogen reduced

versus non-pathogen reduced.

So whether there is some ancillary benefit beyond GVHD for lymphocyte inactivation I think is not clear.

DR. VERDUN: Dr. Benjamin?

MR. BENJAMIN: Thank you. Just maybe to comment on that conversation. What I think, as you know the GVHD work with conventional products really was done 20 years ago. And when the Cerus tried to replicate that data what is most surprising to me was in fact that irradiation is not that effective.

I think there was four (inaudible) reduction of T cell proliferation activity with clear residual activity. And we may not be preventing acute GVHD, but have we ever considered that there may still be some level of (inaudible) that was generated or some sort of subclinical GVHD syndrome that we're not looking for?

There are clearly viable T cells still after our irradiation with gamma or x-ray at this point.

DR. VERDUN: Alright. If we have no further questions I think it's time for our break. And I think we're going to be reconvening at 10:35 maybe. So 20 minutes.

SPEAKER: Those who want to order lunch, there is a kiosk there outside and you can go ahead and order now so that you will not have a long line at lunch break. Thank you.

(Recess)

DR. VERDUN: And so as you can see here, we optimized our storage volumes to doubles, to 625 and triples to 780. We included a 10-ml buffer, because as you are splitting each of the products each one of those products has to quality.

And on this next slide this just shows you a visual representation of what we were accomplishing. The change that we made in RBAX application was to allow for a coding for the pre-treated products, so we had a code associated with the WIPP product.

But additionally, this was an

all-or-nothing approach, because the way our application was configured you either had to have all three or two of the child products go through pathogen reduction, or they all had to go through the conventional process. You could not have, for example, one product be pathogen-reduced, and the other go through bacterial detection. So, that was a nuance of RBAX application.

So what were the results? Early this calendar year we embarked on a small operational trial that lasted about six weeks, the results were very positive, as it related to the trials. So we had roughly 65 percent of the platelet products were now needing the guard bands, up from 5, and then going up from 11 to 12 percent.

Interestingly enough the need to pre-split the products was largely obviated by going -- sorry -- the need to do volume reduction was largely obviated by going to pre- splitting. We rarely reduce the volume of our products at this point. The actual -- and we'll show you more data in a second -- but the actual number of

products as we bore this out, and as the volume increased, was below 50 percent in terms of the number of products that we actually labeled.

And there were a number of reasons for this, because I think as all of you are aware, as you expand your operations, you're going to see other things come to light but low volumes did not materialize. So, we had staffing issues. We didn't have the staff in the right place.

As you will see the labor involved with this activity is significant, so that changed the process of receipt, because suddenly we're eating up a lot of the 24-hour time preparing the products. So suddenly you had a number of products that exceeded the 24 hours, either because they didn't come in on time or -- would potentially exceed the 24 hours, or we didn't have the staff in the right place.

We also saw an increase in aggregates. All of these things we were able to mitigate and manage, so none of them are insurmountable, but they did account for why we didn't see a sudden

massive uptick in the number of products that were actually produced.

So, now the concentration, and this didn't come across the way it looks. So, essentially the darker concentration in the three bands are now where we are able to have them meet through mitigations, the guard bands. The outlying products are, still, what is part of the real estate that we're continuing to look at, how we can draw them into the guard bands.

In terms of our production trend, it is growing. Our goal is to get above 50 percent in every single one of our locations. The important thing is that it is a positive trend, and it will continue to grow, and like with Dr. Snyder, we ended the data in October, because we're still in November.

So, let's talk about the impact of the mitigations quickly. This doesn't affect the hospital customers that we supply, that it is a nuance from operations. We saw a radical shift in our kit usage, so that was an operational issue

for us and also the vendor.

We went from virtually no small-volume kits to the majority of what we produced are small-volume kits. Large- volume kits remained about the same and we just reversed our position on the dual-storage kits. So, that was an inventory management issue, it was also a supply issue, which, all has been remedied now, but it was a transitional concern.

Split rate, the do-no-harm piece. We did see a radical drop in our split rate based on our approach to getting more units to qualify. Part of it was the choices we made in collections, part of it was also the downgrading of products by choosing to pathogen-reduce the product, if we had left it in a traditional path, it might have been a double, but in the PRT path it would up being a single.

The bottom line is our split rate reduced to 1.3, with the optimization of volume and some of the other mitigations we've put in place, we've clawed our way back up to 2.1. So,

this was a positive outcome.

Labor, I inferred -- or implied a little earlier that there was an increase in labor. Based on some early time studies, when you take the standard process with just one bottle -- (inaudible) one bottle for BacT, it was about an 11.1 increase -- 11.1 percent when you looked at an unmitigated pathogen-reduction process compared with non- treatment. And we essentially doubled the labor requirement when we looked at adding the additional steps for mitigation.

The good-news story, however, was that as the volume increased or productivity increased significantly, and we saw 52 percent increase in our productivity. In conclusion, pathogen reduction product remains -- pathogen-reducing 100 percent of all products remains a challenge. It's not impossible. There are choices that have to be made. For the American Red Cross, we're working our way up the chain but, you know, without making radical chances in terms of your split rates, with the current guard bands, it continues to be a

challenge.

The mitigations required to meet the guard bands are feasible, but they are labor-intensive and time consuming, and that you have to go in and know what your process is, and make both the staffing and the timing adjustments, and in some cases transportation adjustments that would involve mid-drive pickups. So, part of what we look at is, you know, we'll say in order for a product to meet all of the pathogen-reduction requirements, you know, the product has to arrive at 16 hours, no later than 16 hours post-collection, so that we can do all of the steps that we need.

And as most of you are familiar with production, every time you touch or adjust a product, it's not just doing that, you then have to re-weigh it, transform it in the computer system, and it has a number of steps involved.

And you, big lesson learned, I already covered this, is that there is a lot of involvement with our collection staff. We are

very fortunate to have a team of excellent technicians and educators in our collections world who worked with our collection staff, and one of the positive outcomes from this is that they created essentially, a programming boot camp, that they put every single collections person through, and then have at each location, localized experts where they go in and they run scenarios over and over with them. So there's less variability in the programming, and they look at the different variables that are presented with the donor and make the wisest choices to optimize split rate and make more products qualify. And I thank you.

(Applause)

DR. FLEGEL: Thank you for the presentation, and the questions will be -- can posed during the panel discussion at the end of all five presentations. So, where are we?

So, David Reeve presented the implementation at the largest blood service here in the U.S., and I give the impression how we implemented it at the hospital-based blood

centers, and I'll also addressed briefly, how the acceptance by the hospital staff was experienced.

So, I share one hospital blood bank implementation of pathogen-reduction produced platelets. I tried to show what kind of challenges we had to overcome to implement that in a smaller hospital-based blood bank, and you may also observe the potential impact of pathogen reduction on the availability of the platelet inventory.

I have no disclosures relevant for this presentation, and everything that I preset is on the label, and no off-label use. And by way of introduction, the NIH Clinical Center at the NIH but that's -- 20 minutes drive from this place is the nation's largest hospitals devoted entirely to clinical research. And we have about 1,600 studies ongoing at any time, and most of them are Phase I and Phase II clinical trials, and NIH is part of the Department of Health and Human Services, just like the FDA. And we're funded by NIH intramural grants and cannot compete with

(inaudible) NIH extramural grants.

The Department of Transfusion Medicine is the full Blood Bank at the NIH Clinical Center, it collects and prepares whole blood at apheresis platelets granulocyte plasma, cryoprecipitates as well as, of course, cellular products. There are several sections within the Department of Transfusion Medicine, and the transfusion services section along with the blood donor services is mostly involved in preparing those platelet that we're discussing today.

In the fiscal year 2016 which was the year of introduction of the pathogen-reduced platelets, we had about 670 patients actually transfused, with 4,000 apheresis platelet transfusions, 5,000 red cell transfusions, 600 plasma transfusions, and 59 granulocyte transfusions.

There are a few major changes that occurred in the past 10 years in regards to the platelet product -- of the products used. So since 2009, we moved to 100 percent

leucocyte-reduced red cell transfusions, in 2014 we changed our red cell supply to the effect that no red cell unit older than 35 days is transfused. And in 2016 we introduced the pathogen-reduced platelet products I'll discussed and for the rest of my presentation.

Before 2016, we had apheresis platelets suspended in 100 percent autologous plasma, five days shelf life, and 100 percent irradiated with 25 Gy. The precautions to prevent contamination by bacteria are the FDA mandated with a variation using a different system that, however, was coordinated with the FDA.

The new process since January 2016 is that we are using InterSol platelet additive solution, and combined with the INTERCEPT, which is the pathogen-reduction process, or pathogen inactivation process, as I learnt today, and that was extensively discussed in the first session.

To introduce that we first evaluated our collection data for six months in retrospective fashion for about 1,000 successful collections,

and compared that with the INTERCEPT guard bands. And the conclusion of that evaluation was that almost 100 percent of those collections met the guard bands' specification overall, and those with that followed in the guard bands of the dual storage kit, which was addressed in the previous presentation. And they have three different kits, and one of them is a dual storage and was -- mostly fell within those specifications.

And the conclusion was that we will use dual storage kits only. We had to adjust the parameters of our collection for about 5 percent of those collections, so we had to talk with the blood collection folks in the Department to adjust that, and we estimated that the possible loss should be less than 1 percent of all collections. Now that we do that, the INTERCEPT System was approved in December 2014, almost exactly four years ago.

In January 2015 the NIH decided to implement that technology at our hospital, an agreement was then signed between the company and

the NIH, and the implementation team was created in June 2015. We made computer upgrades to accommodate changes; that's actually a major component that one has to consider early on, and as we learned later as well, this was a big step that has to be considered.

We started in August 2015 with training of the technology in the section, the InterSol training was then also introduced, and the first product was actually produced on January 11, 2016, more like almost three years ago. And after the introduction we still have to do the validation, which then eventually was signed off in February 2016, one month after the introduction of the first product.

The task to get started is to write the validation plans and SOPs, order equipment, reconfigure the space, a little space is needed to introduce that into your service. We have to train the staff on the pathogen reduction process as well as the additive solution collection.

And most importantly, we have to

fine-tune the collection parameters to meet the guard bands; that's very similar to the situation of the American Red Cross, just with smaller numbers. Before introducing then the product one has to inform and educate the clinicians, the nursing staff as well as the external customers. They have to adjust the collection parameters, validate the pathogen-reduction produced platelets, and we could eliminate the irradiation.

At that time you still have to ask for variance to do that, however, since March 2016 a change was made and one does not need to ask for that change any more.

So what are the critical steps? One has to begin within 24 hours of collection, the product must contain less than their number of red blood cells shown here, that's usually not a problem with apheresis products, what is the problem is that the product must meet the defined guard bands in regards to volume as well as platelet yield.

And that can be done, but one has to

coordinate that with the collection staff on an ongoing basis, essentially with every collections you have to make sure that you stay within those limits.

This shows our pathogen-reduction corner, it's the usual government quality infrastructure, (laughter) but it works, it works. So, we educated and notified the external customers, we don't have too many, and that was very easy, and we didn't get any calls on that. We noticed the prescribers in our hospital, this was sent through the Office of the Deputy Director for Clinical Care, so we used that, that they listen to us, the focus was on improved patient safety, and included the circle of information.

They were instructed to call with questions, and some did, and we explained a little bit why this was done, and how it works. We noticed the nursing staff, I think that's a very important step involving the occupational leadership of the nursing section. And we showed, and I will show you in a moment, some slides on

how the new and the old bags look like.

The electronic transfusion documentation was implemented and showed how it worked, and there were no questions from the whole Nursing Department. At the time when we introduced these kits Zika hit the shores of the United States, and although there perhaps was some grumbling about the cost and whether it's necessary to introduce this pathogen-reduced platelet technology at the hospital, once the virus was discussed, the advantages became immediately apparent, and there were no questions anymore.

So, this shows a comparison of the old and the new platelet bags, so that helps if you want to implement that at your hospital to show how it differs, and what needs to be considered. In particular one of the biggest difference is the point that the old bags without pathogen reduction needed to be irradiated, and the new ones don't. But you will have stock to -- to inventory, and it's critical that the transfusionists are aware of that distinction, otherwise it would seriously

put patients at risk, and we want to certainly avoid that.

Then this is a closer look to the new label which shows that it's with additive solution, as well as the inactivation by the psoralen treatment. The ongoing activities, that we still have to make sure that we have timely platelet counts because they're needed to adjust the collections accordingly. In theory it should be possible to do that for a 100 percent of all collections in practice is still a challenge that needs to be done, and done on a daily base.

This is in an effort to reduce the guard band failures which causes waste, and also puts stress on the donor who goes through the process, and then in the end blood bank -- the blood product can't be used, and that we really should avoid that, also in respecting the donors' efforts.

The transfusion reactions that we observed didn't change much. There's no clear trend, certainly no increase of transfusion

reactions reported with platelets over these three years, or compared to the year 2015, which was without the pathogen reduction technology, and without the additive solution.

This shows the impact of the guard bands, or how we managed to cope with the guard bands, and perhaps a little busier slide, a busier slide of my presentation, though in total we collected almost 6,000 apheresis product, and outside of the guard bands and therefore that couldn't be used, were a total of 200.

However, if you compare the third line here, then initially, when we introduced it the failure rates were quite high, and surprisingly high. And we had -- we went through a learning curve to accommodate for the guard bands and to make sure that the failure rate is lower. And we managed over the years to get to less than 3 percent, and in the latest quarter here, it's actually at 1 percent, where we want to have it. The last line shows the retention of the platelets which is actually above 90 percent for a quite

large number of platelets that we test in our Quality Assurance Program.

So these are our wish for the future. We would like to see the pathogen-reduced plasma products, not only platelets, but also the plasma that in theory is available here in the U.S. as a licensed product, but we don't have it implemented in our hospital as of now, but we're moving to that point. It would be helpful if the guard bands could be widened, that's a question to the supplier of the product obviously.

It will certainly cost an effort to make that happen, also to get the approval eventually by the FDA, but it would have a large impact nationwide, because it would make the implementation of the technology much easier and eventually cheaper.

We hope that some travel deferrals could be removed one the inactivation technology is available. And then a word of caution here, I consider the personnel effects when introducing the product. It's not only the real estate that

you need for the instrumentation, but also the personnel.

There are some personnel savings, less work, because some topics can be dropped once you have introduced this technology. However, our experience is that in the end it is more a personnel-required, and no one wants to consider that perhaps during the introduction or for the consideration when you introduce that at your own hospital.

In summary, the NIH Clinical Center, transitioned to the production of the pathogen-reduced platelets in January 2016. The whole process took about one year. It could be done faster, but that's probably a good timeline when you consider introducing that in your blood center, an important step for the acceptance in the hospital is the education and notification of the nurses and physicians.

And in our case it overlapped with the occurrence of a kind of new pathogen to the U.S., which has certainly helped in the acceptance of

this product. It's all about improving patient safety, pathogen reduction enables the safety that is critical for many patients depending on those transfusions and the quality of their life. It's obviously effective against majority of bacterial viruses and protozoa. It also gives a much wider margin of protection against transfusion-associated graft-versus-host disease. I think in particular this aspect perhaps could be investigated and stressed a little bit further, and particular when it comes to the irradiation of red cells where we are eventually moving, or pathogen reduction of red cell product.

The current 25 Gy borderline harming the red cells already and can't really increase it, and at the same time the Gy are kind of the lower limit of what is needed for patient care. And this whole problem would be totally removed the moment that pathogen-reduced technology becomes available for red cell.

It's not, obviously, the most simple or cheapest, but it's the right thing to do. That

would be my conclusion. It takes a village to implement it, and these are the names who, and the sections who were involved in the introduction at the NIH Clinical Center. And I think you very much that they collaborated so smoothly to implement this technology three years ago.

And at this point, I'm concluding my presentation. And we are moving to the third presentation by Dr. Dana Devine, from the Canadian Blood Services. Who is now discussing the impact of this technology on platelet quality, count and clinical implications.

Now, somehow I have to get that done. That's yours, right? Okay. That works very well.

DR. DEVINE: Okay. Perfect. Thank you. Thanks very much. And thank you to the organizers for the opportunity to speak with you today. I was asked to cover this topic, which is: What is the impact of pathogen-reduction technology on platelet quality, platelet count? And then what are the clinical implications of all of that?

So, I will try to do that for you. I

have just disclosures, I don't currently have active research support, but I have within the past five years, from three organizations that interested in pathogen activation technology.

What I want to do really is just cover two topics. One is really looking at laboratory investigations of the effect of pathogen inactivation technology on platelet quality, and then to talk a bit about what we understand at the moment about the clinical assessment of platelet functions after those platelets have been subjected to pathogen inactivation treatment.

So, I had assumed that by the time we got this far into the program, someone would have actually covered off the biochemistry of how these things work, and that hasn't happened, much to my surprise. So, I will probably be talking a bit more than I had originally planned about actually how these things work, because that's important to understanding what their impacts are on our laboratory results.

But let's go back for a moment and just

look at, you know, what are we actually doing when we pathogen inactivate a blood product. These technologies are agnostic to the source of the nucleic acid, so the pathogen inactivation technologies are going to have an effect on all treated cells, not just the invading bacteria, or invading viruses that you're trying to get rid of.

So, we have to balance the ability to kill the pathogen, with the killing off the transfusion cells, and so this is the scenario that we're trying to work with. The quality parameters that we measure in components are actually expected to change because you know that with this balance, you're going have some effect on the human cells that are in that plastic bag that you've treated.

So, when you're thinking about your risk mitigation for your infectious agents, you have to consider both what the actual risk is, but also what the risks are to the product efficacy, and it's really that balance we need to think about. So, we have to start from the premise that there

will be an effect, and so we don't want to ever start saying, well, you know, we don't want to influence pathogen inactivation technology, because it might do something to the product. It's going to do something to the product. That's the table stakes.

So, let's look at actually, what does it do, and I'm going to focus initially on laboratory studies, and I wanted to say a word first of all about, if you're the producer of platelet components, what kinds of things would you expect? So, we know we're going to see some loss of platelets, and why is that happening? Well, that's happening simply because this is a more complicated production system, than what we currently do to make a platelet component.

So, we prepare a platelet component using conventional technology, and then we're going to take that bagful of platelets and start messing around with it. And the messing around with it in all of these systems, involves transfer of those platelets out of a storage container into

another storage container, or a second or a third.

Every time you remove those platelets from one plastic bag to another you're going to lose some. We all know what the platelets like to do, they like to stick to things. That's their whole role in life. And so when we move them from one plastic bag to another we're going to lose some, they coat the inside of the bag as we transfer.

So if one goes and actually looks at the various technologies that are out there we do see some loss of platelets as we go through the process. Again, this is on the order of 5 to 10 percent of reduction in the platelet count. So, you can anticipate that the product, after you've treated it, will have fewer platelets in it than what you started with.

And so when you're producing these components, you need to accommodate for the loss, and that should keep you from ending up with platelets products that are below your minimum platelet count, and therefore would fail your

quality control testing for count. So, this is an adaptation that has to be made in the production environment, and I'm sure that our first speaker in this session can tell you chapter and verse about how one has to go about making those accommodations.

Let's look at the actually effect of the pathogen inactivation treatment itself. So, we know that these processes are going after nucleic acid. Well, platelets actually don't have a nucleus, we all know that, but they are full of RNAs of various sorts, and not very surprisingly, if you treat the platelets with pathogen and activation technologies, this is the Mirasol treatment shown here on the left, you will see that you have -- and you look at the residual messenger RNA-contained platelets, that you actually are dropping by a log, the amount of residual message inside platelets.

Well, do you we need to worry about that? We don't know. We just know that it's changing. We do believe that that messenger RNA

and platelets are there for a reason, we do know that platelets synthesize proteins. We don't know what the actual effect is on the cell biology of the platelet by losing 90 percent of its messenger RNA, but we do know that not all messenger RNAs are affected to the same degree.

So, there's variability there. And we also know that, similarly, this example on here is looking at a micro RNA, that micro RNAs are also affected by treatment pathogen inactivation technologies. So, this is completely expected. This is how these technologies work. So none of us should be surprised to see this.

We can see the cells respond in other ways, and the actual biochemistry behind all of this is not fully sorted out yet, but we do know that if you go in the laboratory and you look with the typical kinds of assays that people who study platelets and plastic bags look at, you do see effects of pathogen inactivation on most of the measures that we make.

So, this just happens to be INTERCEPT's

treatment, but this is not an INTERCEPT issue, this is true for all of the pathogen inactivation technologies that have been developed to date for platelets. And you do see, over the storage time, after you've treated them, that you start to see an increase in the amount of activated platelets as measured by the P-Selectin expression, and greater than what would happen in platelets that had not been treated.

These happened to be pool-and-split studies, so this is not a donor effect, this is actually a treatment effect. Similarly if you look at -- sorry -- I should have taken an automation of slide. If you look at the Mirasol technology you see something very similar that you do see an increase in the amount of activated platelets as a response to the treatment.

This is probably mostly mediated by the exposure to various UV radiation, and that this causes, at least in this particular study, enough of an impact that you're starting to, by day seven, to drop those platelets down to a pH that

is a bit worrisome.

It's not just activation markers on the surface of the platelets, if you go and look at the cytokine release and treated platelets. You'll also see that for every -- for the four that are measured here, for every pairing that you look at, so here's a day seven of a control, and then irradiated again in the pool-and-split model, so this is not a donor effect, you see an increased amount of release of various cytokines in platelets that have been treated with pathogen and activation technologies.

So we know these technologies have an effect on the platelet. Is this good or bad? We're not completely sure, but we just know that there's a difference. So, the take-home messages for the laboratory analysis, is that we, yes, the use of pathogen inactivation technologies does cause changes in the responsive platelets, in in vitro assays that look a whole lot like the platelet storage lesion, but not exactly like the platelet storage lesion.

One question we have to consider is whether we actually are using the best test to perform quality monitoring of pathogen-reduced platelets. We just took that laundry list that we use for regular stored platelets and flipped it over and are looking at the pathogen inactivation platelets. Is that the right set of tests? We don't actually know that. So that's one area in which we're really lacking good information.

We also have to not equate the in vitro laboratory markers with clinical efficacy of the product. This is an easy tendency to do as you see a change of that, it looks like something we ought to worry about. I'm sure it's going to have a bad effect on my patients. We need to actually know that with the data not just to make that extrapolation.

So, let's actually look at some of the clinical assessment of pathogen inactivation on platelet function. And I'd just like to step back and say that we knew all of this from the beginning, and then we won't be surprised when we

actually look at clinical patient studies. So, in order for any of these products to get licensed, there are clinical studies done.

And if we go back and look at them, we can see effects of the pathogen inactivation treatment. So, if one looked at survival and the recovery studies done in normal volunteers when these technologies were first being developed, you can easily see in the data that are in the literature, that pathogen-reduced platelets have a 15 to 25 percent decrease in survival and recovery.

So, here's the demonstration of this increase in activation and the changes that are caused by the actual processing. The table that's here happen to be the results of the two Phase III clinical trials, euroSPRITE and the SPRINT trials done for INTERCEPT, and what you see here is that you do in these -- so here's control and here's test where you can see that there is a reduction in the platelet dose which we talked about, because you're moving the platelets from one bag

to another.

But you also see some decrease in the actual transfusion interval that relates to a shortening of the circulation time of those platelets in the patient. So, none of this is a surprise, this has all been in the literature for quite a long time, and so we know what the effect is going to be of these platelets when we give them to patients. So this is the tradeoff that we're making for the increase safety, and it may bean that we need to think a little bit about exactly how we operationalize our transfusion practices in this group.

We started to accumulate enough papers in the clinical literature now that there's actually an opportunity for folks who are very good at going back and looking at all of these papers together and saying: what is the literature currently telling us? And this past April in Amgen Oncology, Lise Estcourt from Oxford, actually had this nice little -- this is a two-pager, it's very easy to hand around to your

clinical colleagues who want to know what's happening with the platelets.

And she just asked the clinical question against the existing literature: are pathogen-reduced platelets as effective as standard platelets in the prevention of bleeding of people of any age who require platelet transfusions? And what we see right up front, is that when you go assess the literature, we all do these studies in stable hematology oncology patients. So, we've got a problem right up front with the literature that is available to do these kinds of rigorous, high-quality evidence trials with.

However, what the bottom line here was that if you have someone that is receiving platelets because they have a low platelet count, and this is part of their therapy, that the treatment with pathogen inactivation technology does actually cause a slight increase in the risk of platelet refractoriness, but overall, as someone has said earlier this morning, doesn't

seem to cause any change in the patient mortality.

So this is a safe product from that perspective, and that when one goes and looks at all this summarized evidence, there's not any indication that pathogen-treated -- or pathogen inactivated platelets have any increased risk of significant bleeding, so WHO's grade three or four type bleeding does not seem to be different. And so there's not a serious adverse event risk associated with the product. So, that's very comforting. There obviously are some other changes that need to be considered.

Interestingly in the same issue of this -- of the journal, was the report coming from the French group, who had done a very large, randomized clinical trial looking in the three-arm study at INTERCEPT traded platelets which are in, as you had heard earlier, are in a PAS-C, a platelet additive solution called InterSol. They compared that to platelets that were in InterSol alone, and compared those to platelets that are suspended in plasma.

And this was, again, as was also mentioned earlier, another non-inferiority study, which is how we tend t look at these things, and the primary outcome was a grade two a higher bleeding.

This study which goes by the acronym of EFFIPAP, obviously we need to teach the French about how to make their acronym have some catchy word, because this doesn't mean anything in either English or French. But what they were actually able to show was that non-inferiority was not achieved when they compared the INTERCEPT pathogen-reduced platelets in additive solution to untreated platelets in plasma. So, the issue here is if you change two things, you actually have made a bigger change that you would expect if you just change one thing, because if they actually looked at their platelets in additive solution compared to treated platelets in additive solution, they were able to achieve non-inferiority.

So, it was not the pathogen inactivation

process itself that was causing them the trouble, it was the combination of additive solution and inactivation compared to platelets and plasmas alone. So this was an interesting observation and it probably means that we need to be thinking a little bit harder about the platelet additive solution side of this equation.

Just to mention, someone had said something earlier about the PREPAReS trial, this is a Mirasol-based study, trying to do something quite similar, and this was actually looking at buffy-coat platelets, the whole blood-derived platelets that are used almost everywhere else in the world except here, and what we -- what that study was able to do was to compare platelets and plasma versus Mirasol-treated platelets and plasma. So this was, there's no additive solution in this set of studies.

It was started quite a long time ago by the Dutch, and then our organization, and the Norwegians piled in to help get the study finished. It was just recently published, and

what that -- what PREPAReS actually showed was that pathogen inactivation platelets were non-inferior in preventing bleeding only in the intention to treat analysis but not in the protocol analysis.

A little bit unclear why there are a lot of protocol violations in the Netherlands, and that may have contributed to this issue. But also importantly there was some hope that there would be a different scene in alloimmunization rates between treated and not treated platelets, and there were no differences. So, that wasn't going to work.

What about patients who are actively bleeding? Well, this has been raised earlier today as well, but the question really is, if you start filling actively-bleeding people, full of a whole bunch of products that maybe aren't behaving quite the same as the untreated products, are we going to end up on a problem.

And so, John Hess has been asking this question, and had put this interesting table

forward, where he'd done by mathematical calculation asking: if you keep messing around these blood products what are you doing to them? And essentially, you say that, well, if you have normal blood that we haven't even bothered to collect out of the arm yet, but definition, our effective coagulation activity has to be 1 international unit per mil, and against a typical platelet count of 250.

And then he said, okay, I'm going to go mess with this and make components, and then I'm going to treat those components, what's left functionally? And you can see that as you move into a typical massive transfusion protocol scenario, you're losing coag function and you have fewer platelets available. So, this is sort of what we knew. And then John went back and calculated and said, okay, if you're looking at reductions in fibrinogen function, et cetera in pathogen- reduced products, you get yourself into situation where you're moving even further down this curve.

And he just posited the question: are we actually -- Do we need to worry about this or not? And the reality is this, that we don't actually have any direct studies that asked this question in a proper, high-evidence, RCT-type controlled manner. But we do have descriptive studies, and they have at least to date, not identified any problem in this area.

So, we have countries in the world where all of their platelets by law are treated with pathogen inactivation, and as those folks in those countries have gone back and looked at their data, they're not actually seeing differences. So, that's comforting, but we're also still missing the high- quality evidence piece.

So this is mostly for Simone. I thought I'd put my two cent in here, about what gaps I think the research world needs to fill. I do think that we need to determine whether we can develop strategies to minimize the damage to platelets and also to red cells, and this may be about different additive solutions.

We think that we're -- at least in the platelet world, the newer additive solutions seem to be doing a better job, so a PAS-E is better than a PAS-C, and that may improve the ability of pathogen-reduced platelets to withstand the typical storage conditions. Like, we all want at least seven days, right. That's what we want. We don't want to have to keep throwing platelets out after five days, but we need them to be in reasonably nick in the end of that storage period.

As I mentioned earlier I don't think we've actually thought our way through what kind of quality control measures we need to be using for pathogen inactivation platelets, we just transferred the other ones over, and I'm not sure that's the right thing to do. We need to understand this question that's been raised by the trauma community. Is this going to be a worry that we're going to be infusing lots of different kinds of pathogen inactivation treated platelet products in trauma? And we need to understand that.

Do we need to adapt transfusion practice to accommodate these products, so we know that we have a shortened intra-transfusion interval, we all have practices that are a habit. You go in the morning, you have platelet count, the transfusions are ordered. This is all very rote in most of our institutions, unless someone starts to bleed. But do we need to actually look at how we do that, so that we're optimizing how we actually use this new product?

And then I think, very importantly, we need to really have a conversation about how we best calculate the risks and the benefits of pathogen inactivation, because this is an expensive technology, and it may actually result in increased platelet use despite Dr. Snyder's slide, but he may have another explanation for why his graph continue to go up, in and upward direction.

May be just hospital practice, but it also just may be that the data that are coming from the controlled trials that are showing some

increased use of blood products, we need to understand what that means, particularly if you work for an organization that produces the things.

So those would be some areas where I think that, as a community, we still have quite some lack of understanding in some key areas, but with working together we certainly can address them. So, thank you for your attention. And I will get off here, and the next person can do their thing.

(Applause)

DR. FLEGEL: Thank you for this presentation. And we move on to our fourth presentation today by Dr. Claudia Cohn, considerations for implementing solvent/detergent-treated pooled plasma into a hospital system. Moving away from the platelets and getting closer to the plasma. And actually discussing a technology that's available for over quarter of a century, if I got that right, if not here in the US and certainly worldwide.

DR. COHN: Thank you. Thank you for the

introduction and thanks to the organizers for giving me this chance to present on Octaplas, the use of Octaplas at the University of Minnesota. These are my disclosures. So, in this presentation I will talk about -- or provide an overview of Octaplas manufacturing process and then I will talk about the efficacy and safety of Octaplas and the reasons why we chose to adopt it at the University of Minnesota.

Like other plasmas, it's an FDA-licensed pooled or its FDA-licensed product. It's been pooled and solvent/detergent-treated. It is blood group specific. It is provided as a frozen product, that's available in 200 ml bags, are all the same. It is available for three year storage at negative 18 C and after thawing you may use it at -- you may use it for 24 hours, if it's been stored at 16 degree C or eight hours, if it's been stored at room temperature.

It is the all plasma that goes into Octaplas as obtained from US plasma donors. It's all frozen within eight hours like FFP. Each

donor has -- is identified, registered, educated. There is deferral check, there is questionnaire of donation, donors will be excluded if they do not meet criteria and there is a physical assessment. There is -- because the S/D process affects enveloped viruses, non-enveloped viruses are checked and so there is NAT testing for HIV, which is enveloped, of course, B19 though. HIV, Hepatitis A, Hepatitis B, Hepatitis C and Hepatitis E, all are screened for by NAT.

So, this in a nutshell is the process for making solvent/detergent pooled plasma Octaplas. First, all of the units are assembled and sorted by ABO type and then anywhere from 600, roughly, to about 1,500 single units is pooled together by ABO type into a single pool. That's the dilution step. That pooled plasma is then treated with solvent and detergent that will affect enveloped viruses. The solvent detergent is removed by oil and solid phase extraction. And then the units are aliquot into 200 ml bags.

This is a more detailed reiteration of

the general manufacturing process I showed before. I am not going to go through each step but I wanted it in the record. The steps that are highlighted in yellow are the key steps that help to make this a safe process or safe product. The first step showing the pooling of the 1,000 different plasma units. I will be talking about why the dilution is important for safety in a few slides. Cell and debris is removed by filtration and initial filtration step and we have the solvent/detergent- treatment and then eventually sterile filtration.

So, this is an FDA-licensed product for -- and the approved indications are replacement of multiple coag factors in patients with the prior deficiencies due to liver disease, undergoing cardiac surgery or undergoing liver transplant. It is also approved for apheresis in patients with TTP.

There are contra-indications shown in the slightly smaller print down below. If you have severe IgA deficiency, which is of course

true with regular plasma, conventional plasma. If you have severe deficiency of Protein S that's unique to Octaplas. And then if you have hypersensitivity to plasma proteins, which of course is true for all plasma products.

So, when we were considering whether to use Octaplas at the University of Minnesota, we asked two basic questions. Is it as efficacious as conventional plasma and is it safer or as safe as conventional plasma? And we split safety into infectious risks and non-infectious risks.

So, efficacy first. This is FDA-approved because it is FDA-approved it needs to meet certain guidelines. So, the reference range for all the different factors that need to be in plasma and all the basic coag tests that are used to assess patients who need plasma, all met the criteria shown. Protease, inhibitors and cofactors were also assessed and all also met the reference ranges that were stipulated. It is approved for patients with TTP, therefore the ADAMTS13 levels need to be within acceptable

range. So, they assessed the antigen level and activity level of ADAMTS13 and it was all within reference range. And you could see at the bottom that the von Willebrand factor multimers had the same pattern as we see with normal plasma.

There are multiple small, mostly retrospective studies looking at Octaplas versus other plasmas but these are five randomized control trials. Just five of them. They are all fairly small. The largest is the Bartelmaos study with 293 patients. So, these are not powered to be able to say that truly these are efficacious or non-inferior, but nonetheless, my reading, my interpretation of the data was that all of these trials showed that there was no difference in efficacy when you compare S/D plasma to conventional plasma. There is one study that also looked at MB-plasma but I am not including that in this at all. These patients had either liver disease or going for liver transplant, cardiothoracic surgery and there is one randomized control trial with healthy volunteers.

So, as best as could be said from the data available, Octaplas in my opinion was -- had equivalent efficacy to conventional plasma and so therefore could be used for the patients in my hospital who needed it and it would have the affect desired, that is help with their coagulation status.

In terms of safety, looking at infectious risks, clearly Octaplas, I think, has an advantage because of the solvent/detergent-treatment that reduces the enveloped viruses in the product. There is roughly five to six-fold log reduction, thanks to solvent/detergent-treatment for HIV, Hepatitis B, Hepatitis C and West Nile virus. And as I mentioned earlier, the non-enveloped viruses are screened. So, that Hepatitis A, Hepatitis E and Parvovirus B19 are all screened for and there is a significant reduction, log reduction in the level of these viruses in Octaplas.

This is also true for Zika inactivation. This is not -- clinical data, these are just data

from viral reduction studies showing that there is a significant reduction or log reduction of the Zika virus present in this plasma making it safer for patients. And for dengue virus as well.

This is a meeting to discuss infectious risks but I think you can't solvent/detergent-treated plasma without also considering non-infectious risks. So, looking at allergic reactions and looking at TRALI, we can look at the data that are available for S/D plasma. Comparing an infectious risk to an allergic risk many people might say that they are not really equivalent. But for patients they are a big deal. No patient wants to have the rashes, the itching and when it gets scarier, when it becomes a more important reaction the threats the airway.

So, for non-infectious risks, it's all about the dilution. The solution is in the dilution. So, if a patient has or rather a donor has in their plasma some allergen that's going to affect a patient receiving that plasma, say to

peanuts, if that one unit that has that allergen in it, it's diluted a thousand-fold, the risk of having an allergic reaction is reduced or mitigated by the dilution.

This theory is borne out by the data. There are many different studies which compared the risk of an allergic reaction or the rate of an allergic reaction with S/D plasma versus conventional plasma. Very different numbers but all the same general trend in the first study, on the first line Haubelt, there were zero reactions but it's -- there are 30 patients roughly in each cohort. For the Scully study, which is larger in 509 patients there were just 3.1 percent rate of reactions with the S/D plasma and a roughly three-fold increase with conventional plasma. That three-fold increase is seen in the next study by [Tuscon Hakkard] and then you have the next two studies didn't compare, they just came up with a rate, which was fairly low.

The Bost study was human hemovigilance data from France and what they found was roughly a

one and half fold reduction in the rate of allergic reactions in patients on S/D plasma versus patients receiving conventional plasma. When Finland switched from conventional plasma entirely to S/D plasma they saw an 83.3 percent reduction in serious adverse reactions. That number is pretty amazing to me but that's what their data show.

And regarding TRALI, it's very difficult to prove a negative. It's possibly impossible to prove a negative. But the dilution that occurs with S/D plasma also mitigates the risk of TRALI. It makes sense. If there are HLA -- antibodies to HLA or antibodies to neutrophils that are driving the path of physiology of TRALI, if you dilute out of those antibodies, you reduce the risk of TRALI. So, there is the dilution but then after the dilution every batch of S/D plasma is tested to see if it is low enough, if they can detect any antibodies to HLA or HNA. And if they can detect them, then that batch does not go through. So, you have to have a very low level in order to

become S/D plasma.

There are other ways that -- it's not that TRALI occurs. There is bioactive lipids and these bioactive lipids should be removed by the solvent/detergent process and so that also would mitigate the risk of TRALI. And these steps meet the ABB requirements for TRALI mitigation.

So, based on the dilution we look at the numbers and see if that's borne out and indeed in the various countries that are using S/D plasma, they have rates of TRALI per 100,000 transfusions with conventional plasma, in the left hand column in the red box. And it ranges from 1.5 to 8.8 cases of TRALI per 100,000 transfusions, whereas those receiving S/D plasma, it's zero. In France, they saw a 1 in 31,000 risk of TRALI, whereas with S/D plasma, there were zero cases after 200,000 units were transfused. And if you put some of the published data together, in over a million and a half units, there were zero cases of TRALI in countries where only S/D plasma is used. And Jim AuBuchon mentioned also that in 10 million cases

of transfusion there has been zero TRALI. So, you can't prove it but the numbers are compelling. That we are removing a significant risk to patients.

So, the benefits added up for me. We -- the S/D plasma process inactivates enveloped viruses. The level of non- enveloped viruses is reduced by screening. The dilution effect mitigates the risk of TRALI. The dilution effect mitigates the risk of allergic reactions. And coag factors are present at a slightly lower level, albeit a sufficient level for my patients to be able to achieve better coagulation status.

Not every product is perfect. So, I leave this slide up so that you see that there are contra-indications. Some of these, I already mentioned. It's particularly the Protein S deficiency. Whenever we are consenting a patient, we have to add that into the consent process, if Octaplas is being used.

And so, with those key considerations that virus for screening for both enveloped to

non-enveloped viruses occurs, that the pooling helps mitigate risk, that there are multiple filtration steps, that it's been on the market for a long time and that it's always the same. When I use conventional plasma all the different volumes are different and if I am doing a large apheresis, that's a bit of a pain for the blood bank. Having a consistent volume is very useful when issuing plasma. So, for these reasons we decided to adopt S/D plasma at the University of Minnesota for patients who have indications for it. Thank you for your attention. (Applause)

DR. FLEGEL: Thank you. We move on to the fifth and final presentation for this late morning session. It's presented by Dr. Brian Custer. And he will speak on health economic considerations for pathogen reduction technologies.

DR. CUSTER: So, good morning. I want to thank the organizers for the opportunity to present, particularly at this FDA workshop, some aspects related to health economics. This is

clearly a difficult topic. We have already heard some controversial comments this morning about it.

I am going to begin with a slightly different perspective that I want to cover. So, at the pathogen inactivation workshop, the Consensus Conference, it was indicated that health economics, and particularly cost effectiveness, certainly should not be the decision maker. But it contributes information. However, out of that came a further initiative which was the ABO risk based decision making framework which said, there are many different lines of evidence. And you have to figure out information along a number of different lines to make high quality decisions.

And one of those is indeed health economics. It's not going to be the deciding factor. But you have to consider it because there are clearly implications. We do not have all of money that we would like in the world to do everything that we would like to do. So, we make choices. And that's what this is going to be about.

To begin my talk, I will actually say I have disclosures. So, I have received funding from Macopharma and Terumo BCT and the organization I work for, Vitalant, has also received funding. Turns out I am not going to talk about the technologies that those organizations are developing or have in place.

I am going to focus on the two technologies that are approved for use in the United States. I am going to do two things, kind of, talk about health economics in general. Then I will cover solvent/detergent-treated plasma. Going in this order, cost effectiveness and then budget impact. And I am going to do the same thing for Amotosalen plus UV light, going with cost effectiveness and then budget impact.

Now there is a motivation behind that. Really, if a technology is not cost effective, it does not matter what the budget impact is. If it's not doing more good than harm, it should be not be considered as a candidate for adoption.

All right. So, let me get some

information about what I am trying to do. So, health economics really has these two components. There are many different kinds of health economic analyses that you could do. But these are considered the two, sort of, core areas that you need to understand a little about which is a cost effectiveness. Does it actually improve patient outcomes or prevent disease in some way? So, that's cost effectiveness or cost utility. And then secondly, what would it cost to implement? So, what is budget impact? And these are different methodologies that provide different kinds of information that are relevant for decision makers.

All of that then contributes with all of the other information for payers and decision makers about whether one should implement something and what one should reimburse that technology at what level. So, I want to again, just maybe, provide some groundwork for cost effectiveness. This is a summary. This is the called cost effectiveness plane. The reason why

it's important is that you really are trying to assess both how effective is the technology and what is the difference in cost of that technology or intervention compared to an existing intervention.

So, most of the time, what we are doing is comparing an intervention A, as an example that's up here, intervention A that has a certain cost and a certain effectiveness to an intervention B and it's literally that incremental cost effectiveness ratio or the difference in costs divided by the difference in effects, that is the cost effectiveness ratio. A lot of the times, new technologies are both more effective and more costly. And that is why they are up in, what is called, the northeast quadrant. That's when the decisions are a little bit difficult. So, does it -- is it above or below some established threshold such as 50,000 dollars per quality adjusted life year or something like this or is it not.

However, you can absolutely have

technologies that are in different quadrants. And those different quadrants lead to some easy decisions or some difficult decisions. If it is more effective and less costly, it's clearly cost effective and it's already a candidate for adoption. So, structurally there is more going on in a health economic analysis about what the implications are than just simply, what is the cost effectiveness ratio.

The second analysis topic area is budget impact. This is a very different kind of analysis. It's an analysis of expenditures for a program over a short period of time. Typically one to five years. And it does include the effect of any offset savings. It evaluates a scenario rather than a specific action. It includes comparison to the status quo and it often or it should include sensitivity analyses. So, it's really intended to focus on assessing practical affects in the short term. Long term modeling of costs and clinical outcomes is typically considered unnecessary. Costs are usually not

adjusted for inflation or discounted and reductions in healthcare out far in the future are not in the purview. They really cannot be used to offset or justify the initial start-up costs for adopting a technology. So, that's the objective of what a budget impact is.

So, again the two topics that I am going to cover are solvent/detergent-treated plasma. I am going to speak about that first. Here are all of the available results that I could get. The ones that are in bold are for the solvent/detergent- treated plasma. There have been two analyses that have been conducted for Canada and one, that's been published and conducted for the United States.

There are some other technologies shown here. Again, these are not approved for the use in the US and I am not going to focus on them. But this also, for the completeness of the record, is kind of the state of knowledge of various forms of plasma interventions, whether it's solvent/detergent-treatment or riboflavin plus UV

light or methylene blue treatment and what the cost effectiveness is of these particular plasma technologies based on relatively recent studies.

But going into more detail specifically about these studies that have been done in the North American context. The first one is truly, I think, the best example of a health economics analysis that has been done in the blood safety discipline yet. So, if you have -- if you are not familiar with this report and this is a report by the Canadian Agency for Drugs and Technologies in Health or CADTH. They did both the cost effectiveness and a budget impact analysis and it is freely available. And it's an important example of, I think, where we need to go as a field, in terms of making assessments of the health economics of technologies as we start to build evidence that support intervention adoptions or not. This particular analysis found a estimated, for solvent/detergent-treated plasma, an estimated cost effectiveness of 934,000 dollars for per quality adjusted life year gained or 1.3

million dollars per life year gained for an analysis that included Hepatitis A virus and also B19 risk in fresh frozen plasma.

Solvent/detergent-treated plasma was more costly but also did, again, produce a modest increase in effectiveness to generating more quality adjusted life years compared to FFP for the average patient that was reflected in this analysis which was a 50-year old patient. So, those results are around a million dollars per quality adjusted life year. It's quite a different set of results than the two studies that had been published by Huisman and colleagues where for Canada that they compared again to FFP. They found that the results were cost savings meaning the adoption of solvent/detergent-treated plasma would be cost saving in the Canadian system compared to FFP.

Similar results were generated in the US analysis where the results were at 16,000 dollars per quality adjusted life year. There are clearly some very different assumptions that are

underpinning the analyses related solvent/detergent- treatment, what adverse events can be prevented and factors like this that have to be then considered and evaluated when we are thinking about what do these studies tell us.

In addition, as I said, this study did go on to also look at the CADTH report at the budget impact and the -- not surprisingly because S/D plasma is more costly, they found it had a net budget cost to the Canadian healthcare system for adopting it. Nonetheless, I think it was what they in some ways considered potentially tolerable. Having said that S/D plasma is not currently in use in Canada. So, you know, there are things to consider.

So, I think, it's a good example of how information can be generated and what this can tell us. How we then use that in thinking about adoption technologies -- adoption of technologies is certainly another question altogether. But that's the state of knowledge with respect to S/D plasma at this point from a health economics

perspective.

There were some additional analyses that were done as a part of the CADTH report and I want to bring them to your attention because I think they are very important. So, they did classic sensitivity analysis. Scenarios were run under different structures and they were replicated many times. And there was no way that they were able -- so all of the simulated incremental cost effectiveness results were in this upper quadrant. So, it was more costly and more effective. But none of those results approached 50,000 dollars per quality adjusted life year, which might be one decision where you might consider. They were all much higher than that. That's consistent with what we saw with that point estimate result.

Similarly, if you take all of the simulations that were done and you think about what is the probability that it might cost effective under different potential thresholds, the cost effectiveness acceptability curve shows that the probability that S/D plasma is cost

effective is zero percent for all values of QALYs less than 100,000 dollars per quality adjusted life year and only 6.3 percent for a value for 500,000 dollars per quality adjusted life year. So, again there is ways of taking this information and saying, what is the probability we will be cost effective at whatever we decide as our acceptable threshold. And, I think, in blood safety, our acceptable threshold is certainly higher than 50,000 dollars per quality adjusted life year. But what it should be remains unknown and frankly controversial.

So, I put this out again as an example of a report that, I think, really nicely covers that the range of things that you can learn, the insights that you gain in the health economics analysis. And I move on now and the rest of the talk is going to be about platelets and plasma PRT.

So, as with that first table I showed there are a number of studies that had been conducted on different technologies in different

settings and they found various kinds of results. All of those results, typically again, are some placed around 500,000 dollars per quality adjusted life year or higher. So, with that mind that they are certainly, you know, again -- this technology itself even with the clear recognition of the contribution to bacterial contamination, risk reduction, does not approach the traditional cost effectiveness threshold.

So, I am going to spend, again more time specifically now talking about the Amotosalen plus UV light for platelets. And the first thing that I will say is that these are studies that were conducted many years ago and they have some assumptions that that might not be the assumptions that would be appropriate today but they are the available evidence for the approved technology as we have it right now.

So, these are results from overseas. So, these are primarily for Europe. The way these analyses were done is that, instead of looking at an average population in general, we are looking

at specific patient populations and what would be the effectiveness or the health benefit for specific patient populations that started with pediatric hematology oncology patients, adult breast cancer patients, adult coronary or CABG patients, adult hematology oncology patients.

But you can see, if you look at those results across the various life years, is that relatively cost effective technology and a younger patient population, because there is many more life years left for the patients to experience. But as you get to older -- conditions that would affect older populations, the cost effectiveness ratios are decreasing. All this matters and what makes this particular area, I think, so challenging is whether you are doing a buffy coat platelet, whether you are doing apheresis platelets. All of these other factors contribute to what the results in that being in a health economic analysis and makes the -- frankly makes the waters muddy. It's very hard to get a clear answer about what the cost effectiveness is of the

use of these technologies.

All right. So, here are the same results again from the studies that were conducted for Amotosalen plus UV light. Again, looking at first some young patient, [hem-onc] patients, then hip replacements and CABG and then adult Non-Hodgkin's lymphoma. And, as you can see, that there is still this general trend of, the lower the patient -- the younger the age of the patient population, that the more evidence of a health benefit that would accrue. Getting up to some examples where -- again, I am only pointing it out to say there is just this range where different patient populations might benefit to a different degree that in an adult Non-Hodgkin's lymphoma situation you might have a cost effectiveness ratio as high as 23 million dollars per quality adjusted life year for a single donor apheresis products.

So, what is this? This is basically the summary that there is this puzzle. There is this puzzle that we have to piece together about what

is going to reflect a given situation, particularly in the scenario of the US of what is the platelet preparation method? Are we looking at platelet additive solution versus plasma suspension? Can we get a handle on what are the appropriate bacterial contamination and sepsis rates in the patient population in the US? What cost offsets are we really able to think about discontinuing? What can we discontinue? Is it through gamma irradiation? Maybe some forms of infectious disease testing, the bacterial culture itself. All of that has to go into the mix to then form an appropriate analysis.

To just provide some insights, so this is not now Amotosalen plus UV light. This is the Mirasol technology but it is an analysis that we did but we wanted to just say, just that platelet preparation method, whether it's buffy coat versus random donor pool platelet versus a 100 percent apheresis platelets, you get to very different cost effectiveness ratios where if it's a 100 percent apheresis platelet, our estimate was about

two million dollars per quality adjusted life year in this model that we developed, it has its limitations. But for other approaches if you are doing a 100 percent, some form of random donor pool platelets, you have much lower cost effectiveness. Now the actual ratio may not be as shown here. But the relative cost effectiveness of each of these technologies is probably accurately reflected here. So, it's just -- again, it matters, the technology and also what specific set of platelet preparation methods you are using.

So, that tells you a little bit about cost effectiveness. It's kind of all over the map, obviously. The rest of the talk is going to focus on budget impact and this maybe the, sort of, important area where people are really interested in saying, how can we learn? Can we find enough cost offsets to be able to help justify and push, sort of, over the bar, to be able to adopt platelets and plasma PRT? So, this is a recently published analysis really focused --

it was funded, I have to say Sirius. But this was focused on really understanding at an individual hospital level, what is the budget impact if somebody was to move to adopt a pathogen reduced or pathogen inactivated platelets?

And they developed a model that has a number of different steps in it. Again it's supposed to be tailor-able so that depending upon what the initial inputs are, if you are somebody who collects some proportion of your platelets locally versus only supplied by an outside supplier and purchasing them. How you produce them? What type of secondary bacterial testing you are using or discontinuing? What your wastage rates are and factors like this. All get put through this process of collecting data.

And then, really trying to look particularly, in this case in the analysis about whether you are using rapid testing approach, to try to get a longer shelf life for platelets versus using the pathogen reduced platelets. What happens on the course of the timeline, in terms of

the availability of the platelets? Are they a little bit earlier released because you don't have the wait for the bacterial culture results and factors like this? So, I think it's a very nice structure that's been developed for looking at this at a local level.

Again, as with any modeling exercise, there are a number of assumptions and some of those assumptions may need to be improved or data may need to support them. And there might modifications to the work that's been done moving forward. But here are, sort of, the assumptions that went into the costs as they were developed and I will describe what this is actually for in just a second. But it said what the acquisition price was for that hospital. Whether it's a pathogen reduced component, platelet competent, a conventional component.

Those were also put through the process of trying to understand with respect to inpatients there is the DRG system. But with respect to outpatients in the US, there is the outpatient

prospective payment system and what those reimbursement rates are. And so, again from a budget impact perspective, trying to say, if we are able to get reimbursed for a pathogen reduced product at the rate of 624 dollars and 61 cents, that really is a very significant thing that helps us understand that the implications because we can really start to offset that cost by getting a close to appropriate reimbursement for a pathogen reduced platelet component.

So, what they did was an analysis for a mid-size hospital that acquires about 5,500 apheresis platelet components per year purchased from an external supplier that had a scenario of conventional -- 100 percent conventional platelets, a scenario of this rapid testing program. Within each of those programs it was assumed that 60 percent of the acquired platelets are irradiated and 20 percent are CM -- are tested for CMV by the blood supplier, with the remaining undergoing neither irradiation or CMV testing.

These are the results. So, for this

relatively smaller size or medium size hospital, assuming a blood budget of a 130 million dollars estimated around total cost, annual cost, that's shown right here in the center, of about 3.6 million for conventional platelet products, 3.6 -- 3.7 million for a rapid testing approach and 3.9 for -- 4 million for a pathogen reduced components.

When accounting for the outpatient reimbursement, the net annual costs were along the same range. The summary here is that, by going to a pathogen reduced platelet inventory, they estimated that the total cost relative to a rapid testing scenario would be about 6.2 percent more for the budget. So, that might be a tolerable level of increase.

But there are some aspects of this analysis that are certainly controversial, they assumed a fairly high cost related to bacterial sepsis for the rapid testing and they assumed no such cost for pathogen reduced platelets. So, again there are aspects of the analysis that bear

a further consideration in terms of the assumptions used. Even so, I think it's a very nice model, moving forward, for individual hospitals to think about what are the implications as they want to adopt or move forward with platelet reduced -- sorry, pathogen reduced platelets.

Final study I just want to touch on is outside of the US and its Italy. And the reason why I want to do that is that they recently published two budget impact analyses related to, kind of, an odd scenario but nonetheless, I think, an informative scenario for the entire country of Italy. And these are the assumptions that went into the model. So, it's the total number of people who might actually get a platelet transfusion in Italy and the various cost structures that they are talking about. That's not actually what's important. Again, Italy is different than the US and so we expect differences. This is the scenario.

In year 1, they said there would be 10

percent of the platelet supply would be intercept-treated or Amotosalen plus UV light-treated platelets and a parallel supply of Mirasol treated platelets. What they were trying to do was understand what were the budget differential impact for a conventional plasma inventory, an intercept plasma inventory and also a Mirasol treated inventory.

In year 2 they moved up to 20 percent for each of the pathogen reduced preparations and in year 3 it was 30 percent. It's really the bottom line that tells the story. The convention -- just with 10 percent, the total cost to the supply was about 6.9 million Euros. As you move up and you have more pathogen reduced components platelets, it becomes significantly more expensive and then actually even when you get to the point of having about 66 percent of your inventory being pathogen reduced platelets, you are looking at a substantial almost one- third higher cost of your overall budget to be able to implement that. That clearly, at a systems level, is a big budget

impact. So, even if it was a six percent increase at a hospital level overall the healthcare system still has to say, is this something that we are prepared to pay for?

All right. So, I think that it's going to very difficult for any of these technologies to really achieve cost neutrality but that is, of course, the objective. If you could get to that, you would have a either cost neutral or cost saving and more effective technology and it would be a very straight forward discussion.

Some of the other work that's been done, and I am just going to touch on this very briefly, is to try to take and look at some other things like adverse transfusion reactions and modeling based on hemovigilance data, what the outcomes would be and they do see at least based on European data evidence in hemovigilance data of reduced rates of adverse transfusion reactions. Those contribute to a better economic profile for pathogen reduced platelets. And again, I won't go into the details for the sake of time, but I think

it's a good example of the kind of additional modeling work that can be done outside of infectious risks that should be considered if the data are there to support it.

So, in summary, really the results are that for plasma alone, you are still looking at, I think, results in the range of 800,000 to 1.2 million dollars per quality adjusted life year. When you look at PRT for platelets alone, if you are able to discontinue bacterial culture which, of course, the FDA guidance would allow, you may be able to see this get down to something in the range of 250,000 dollars per quality adjusted life year. That's my [Gestalt]. We have to really run the numbers and find out. But, I think, you are really approaching what is definitely considered a cost effective technology with respect to blood safety. And for platelets and plasma, the number is kind of between the two because the plasma cost effectiveness pulls the number up for the platelets.

So, the final slide is this. Is that

each -- of course these technologies, as has already been stated this morning, has different modes of activation. So they have different potential technology specific consequences and also specific health economic profiles. They do have different performance against different specific pathogens and the cost of implementing is different for each of the technologies. This potential for additional component use is certainly there and has been modeled. It's been considered an influential model in previous analyses. But the hemovigilance data doesn't support additional component use in the large datasets that are available for the three countries in Europe in particular.

So, I would say in summary that the -- within the blood safety context the technologies are relatively cost effective. They are no less cost effective than other widely adopted interventions in this discipline. Implementation is likely to require discontinuation of current interventions. Budget gap is likely to remain

unless there is this whole blood or red cell additional technology. And reimbursement of the cost, the full cost of PRT probably remains the most important barrier in the US. This is the literature for reference so that people, if they want to get more information they can and I want to thank you for your time. (Applause)

DR. FLEGEL: Thank you for this presentation. I ask the speakers to come to the podium. And I welcome the audience to present questions. Let me say that the online audience is also welcome to submit the questions and they will be forwarded and we will read them here. We have here the first question.

DR. GOODRICH: Yes. Ray Goodrich, Colorado State University. First of all, I think everyone did an excellent presentation. Thank you for that. Question for Brian, and I think I have asked you this before, you indicate that the analysis doesn't necessarily take into account certain factors, budget obviously price is involved. But for quality adjusted life year

calculations, is the cost of the product involved?

And my question would be -- in two parts to it. First of all, could you do this in reverse and say, at what price point would the technology become cost effective? And secondly, if you factor in a three-component approach or an approach, we are going to be talking about after lunch, some of the approaches involving treatment of the whole blood in separation of the components. How does that change your calculations?

DR. CUSTER: So, yeah. It's a very good question and I guess, before I answer can you run it in reverse. The first thing you have to decide is what is your acceptable threshold for cost effectiveness. As soon as you decide that and agree to that then you absolutely can run it in reverse and say, what would the price per component treated need to be to achieve that threshold. But you can't do that until you agree to what is an acceptable threshold.

As for the issue of broader -- more

broadly considering on multiple component treatments. Again, I think that that really shifts the potential ratio significantly in ways that probably so far haven't really been properly modeled to think about. But I would expect the ratio, again, to get much better.

SPEAKER: My question is about pathogen inactivators. Looks like [expo] systems, Mirasol and intercept were scrapped. They increased safety but they also -- have influence, they are lower in quality. In your research have you tested -- actually the effect is dual, the one is chemical that's activated by light and light itself also has some effective -- obviously should have affect. How much light itself, this how three agents contributes both as inactivation and how much damage it does -- have you done such experiment because I have looked in literature and I cannot found anything solid. Thank you.

DR. DEVINE: Maybe I will try to take that one. The -- what we think is going on, is that most of the damage is actually caused by the

ultraviolet light itself. And the way that you can see that most readily is if you look at the three technologies that are either available commercially or hopefully will be soon for the Theraflex technology of Macopharma, you see fairly similar changes in the quality parameters of the products that have been treated. And so, the Theraflex technology doesn't add anything. It's only UVC exposure and so it's probably the energy that's provided by the ultraviolet exposure that really is causing the problem. But at the molecular level the way that it works is not the same in all three technologies.

MS. YAN: Hi. I am [Hoppy Yan] with Red Cross. I have a couple of questions. The first one is for Claudia. So, I was thinking about the decreased Protein S level. And so, when you treat patients who have a thrombotic disease, like TTP. Do you feel like you need to pre-treat with aspirin or anything else to mitigate --

DR. COHN: No. Patients with TTP are a moving target, in terms of coagulopathy. No. We

don't. We just go ahead and do -- and do the plasma exchange as quickly as possible. As soon as they get some ADAMTS13 in their system, it's better for them. So, no. I don't worry about that.

MS. YAN: Okay. And the data from Europe doesn't show any kind of -- okay.

DR. COHN: No. No.

MS. YAN: All right. Thank you. And then the second question is really for Dana. You know, you mentioned, you know, we need to really figure out, you know, what the clinical efficacy is for -- because we know there are some functional defects that are accrued from pathogen reduction. Right now, you know, our tool seems to be, you know, bleeding risk, grade 2 or 3. And that seems like a pretty blunt instrument. Can we have a discussion about, you know, if you have thoughts on other ways to evaluate bleeding risks and, you know, any kind of finer tools that we may be thinking about or looking at?

DR. DEVINE: Yeah. I think that we have

moved from count to does it actually matter by demonstrating clinical bleeding. And I don't think we have really got other tools in the toolkit. I think we have -- it's become -- it's difficult because of the patient populations that we study this in. So, we are studying this for the most part in patients who have hyperproliferative (inaudible), because we have done something to put them in that condition. And we are giving them platelets because we are worried they are going to bleed. And so our datasets are awash with people who, if Simon's [Denver] studies are correct, probably didn't need platelets in the first place. They weren't going to bleed anyway. And so, trying to find these events and then be able to actually measure differences between them, is extremely difficult. And I wish I had a better idea but I don't.

MR. MCCULLA: I am Jeff McCulla from Minnesota. It's a question for you, Dana. If PRT platelets by all these methods are slightly activated, does this mean they might be more

effective than untreated platelets for acute bleeding?

DR. DEVINE: Yes. So, this is the argument I have been trying to make to John Hess because I actually don't think that -- I don't think this is going to be problem in bleeding patients but the other jury is still out. We have to do the studies. But I would agree with you. I think activated platelets are good if you are bleeding. So, should be fine.

MR. MCCULLA: Yeah. And the second question for Brian, if I can. Brian, there is a huge database in Seattle that you know very well, I am sure. I forgot what it's called. But they include things like disability-adjusted life years and other things like that. Is disability anything to be considered in your all your health economics? I am sure you know the database I am talking about. I just don't know the name of it.

DR. CUSTER: Yeah, I know. I am aware of the institute, the university that has this. Disability-adjusted life years are a similar kind

of construct to quality adjusted life years. But they are calculated in a different way based on some different assumptions. It's a bit of a complex topic. But the -- I personally think that for the kinds of medical decisions that we are looking at in the developed countries, quality adjusted life years are more appropriate than disability-adjusted life years which are little bit better in a developing or transitional country setting. But anyway, the database is the institute -- the Institute for Health Metrics and Evaluation has huge a compendium. They are trying to really develop methods and that DALY concept has come directly out of WHO anyway.

MR. MCCULLA: Thanks.

DR. NESS: Paul Ness from Johns Hopkins in Baltimore. And a comment actually for Claudia. And one of things I enjoyed about your presentation was that you did not trivialize allergic transfusion reactions which this world tends to do. Because they are very serious events and we always worry about infectious complications

and don't pay any attention to that.

But in support of what you are saying and the idea of using solvent/detergent plasma, I would think we have probably, at least one patient a year with TTP who we start plasma freezing with routine plasma because of costs -- conscious people don't want to us to pay for the routine plasma. They have serious reactions often getting them into the emergency room or the ICU. We switch them then to solvent/detergent plasma and they get through a course of intensive plasma exchange, very well, with no subsequent reactions. So, I, you know, I think this is something -- it wouldn't show up in a quality evaluation but I think it's really very important for these types of patients to think about that.

DR. COHN: Thank you, Paul. I agree and we have made the same observations. Over and over, we start a patient on plasma. They have serious allergic reactions. We switch them to S/D plasma and they are fine. So, it's very nice, as a clinician, to be able to do that for a patient.

DR. DEVINE: Maybe I just add to that, Paul. In Canada, we actually -- despite what Brian told you, we actually do use S/D plasma but in a very restricted way. So, governments having commissioned that lovely CADTH report that looked at that and said oops, there is a very big price tag here. We don't want to pay. However, they do allow us to provide S/D plasma for patients for therapeutic plasma exchange, who are showing any evidence of having allergic response to plasma.

DR. NESS: Sounds like a very advanced response. Actually the question for Mr. Reeve. With one -- pathogen inactivation was originally proposed to hospitals by the Red Cross based on pricing information, early on. I assume, based on your estimates of the kit costs and your estimates of the labor, I assume that's gone up substantially as a result of all of these mitigation effects. And I wonder what you think that might ultimately do to the deliverable price of pathogen reduced platelets?

MR. REEVE: We are still studying the

total impact of that because we are -- our goal is to mitigate the cost as much as possible and not just pass it on because it -- we believe that through more experience, we can gain additional efficiencies and so we running now some additional time studies where we have got higher volumes and more experience.

DR. NESS: Thank you.

DR. FLEGEL: Sorry. There is one online question here. It was in line before you.

QUESTIONER: So, the question is for Red Cross. And it is, how cost effective it is to treat more products and overall split rate has increased? However, having to treat more use like multiple collection is also expensive. So, how have been like -- or split level as well as multiple collection? Like more collection.

MR. REEVE: Yeah. Yeah. Yeah. So, we are not increasing our collections to pathogen reduced. We have maintained our collection rate the way it is. Our responsibility was to get our split rate back up. Fortunately, when our split

rate decreased significantly with pathogen reduction technology, we were dealing with very small volumes. So, the overall impact to the platelet supply was, I wouldn't say negligible, it was minimalized. So, now that as were experiencing higher volume of PRT or pathogen inactivation treatment, we are back to a normalized split rate. Did that answer the question?

COLONEL CAP: Thank you. Thanks very much. Great presentations this morning. So, Andre Cap from Army Institute of Surgical Research. Dana, I agree that activated platelets are the way to go for bleeding. But the other question I have is regarding the S/D plasma and the significant lack of alpha-2- antiplasmin. In the trauma scenario which, you know, actually accounts for quite a few bleeding patients, fibrinolysis is really a core element of the coagulopathy of trauma. And I am concerned that all this data from Europe that, you know, evaluates sort of huge numbers of patients without

really examining trauma, per se, may lead us to some early conclusions about the safety of S/D plasma where we don't actually have the data adequately parsed for trauma patients who are experiencing fibrinolysis. I think it's an area of research that needs to be further explored. But I would be curious to hear your thoughts on that.

DR. DEVINE: So, some of the hyperfibrinolysis worries came from earlier versions of S/D plasma. They adjusted the manufacturing process and since that adjustment all studies have shown equivalent levels of hyperfibrinolysis in various patient populations. These are not trauma patients. These are all liver transplant patients that always have a high level of hyperfibrinolysis. So, it doesn't address your question exactly but it reassures me that I worry about it less.

COLONEL CAP: I mean, we actively treat fibrinolysis in trauma patients in addition to giving them plasma and what not. And so, I think

it's an area of research that, you know, certainly to reduce allergic reactions. Things like we are talking about in (inaudible) and so forth. Totally different ball game and probably one size doesn't fit all. But this is something that I think before we, sort of, lead towards S/D plasma, at least deserves more study.

DR. DEVINE: I think it will nice. Thanks.

QUESTIONER: You know, my question is also for Claudia about the actual experience at University of Minnesota. So, it's a two part question. First, what percentage of your plasma is S/D versus other plasma? And secondly, the practical restriction of only being able to keep that plasma for 24 hours, according to product insert, how has that impacted? How do you manage that aspect of the issue?

DR. COHN: So, it is a fairly small percentage because we are very aware of the bottom line. So, we tend to chart it out only for patients who have a history of an allergic

reaction or start to have an allergic reaction and we know that we are going to be treating them with plasma repeatedly due to apheresis. So, it's fairly small and as a result, the thawed plasma doesn't enter into the equation very much.

QUESTIONER: I would like to make a comment on Dr. Devine's presentation. Two things. One, you mentioned a five to ten percent loss in the processing with any pathogen reduction process with moving from bag to bag. And that is correct. The only proviso is that with bacterial guidance that we expect in the US, it's very similar to the loss you would see in moving to a high volume bacterial testing with aerobic bottles et cetera, especially if you test every split unit as the British do. So it's a comparable loss. So, I think we are in for that anyway.

The second comment was on, you quoted the [GA Dan] paper, the [Fe PAT] paper. And perhaps I should put that -- that paper needs a little bit of critical appraisal. It concludes that they fail to show non-inferiority between the

past intercept platelets and the plasma conventional platelets for grade 2 bleeding.

As you know there are two ways you can fail non- inferiority. One, you can be inferior or you power -- your study is not powered to show non-inferiority. That study was very poorly powered. It had 80 percent power to show non-inferiority. It then did not enroll as many patients as it planned to. And their primary efficacy end point in their control unit was substantially lower than the youth for their power calculation. So, the power -- the study was underpowered to prove inferiority.

So, you have to ask were the intercept platelets actually inferior? Well, that wasn't the analysis. But they did say that the incidence of grade 3 and grade 4 bleeding was not statistically different between the arms. And if you look at their data for grade 2 bleeding, there is no apparent statistical difference there either. They didn't give a p- value. They didn't do the analysis. And if you do a simple

chi-square value there is no difference statistically. So, I think that paper needs to be put in context before it's quoted as a failure of the intercept system.

DR. DEVINE: So, I did not say it was a failure to intercept system. What I said was, it was a failure of the platelet additive solution and I think that's a very different issue.

QUESTIONER: I agree that you can't pass it to [Arthur].

DR. FLEGEL: All right. Let me ask a question to David who is on the American Red Cross. What can you report on the acceptance of these products by your customers? And what is the major or the major concerns, if any that you noticed.

MR. REEVE: The major concern we are having is that the demand is outstripping our ability to supply.

DR. FLEGEL: Wow. We haven't had that in a while, right?

MR. REEVE: And that's part of the --

yeah. For platelets, it continues to be a challenge. But in this area our ability to supply the treated product to meet the demand is the challenge.

DR. FLEGEL: All right. And a question to Dr. Brian Custer. How does this term cost benefit fit into the whole system? You did mention it and maybe we should just drop that term and define it in the context of the cost calculation.

DR. CUSTER: Thank you for the question. It's a bit of a challenging question in the sense there is, what cost benefit means to a health economist which is very different than what people say when they say off-the-cuff cost benefit. Cost benefit is formally analyzing all costs and all benefits in monetary units and determining a ratio of those monetary units of the benefits. And that immediately requires placing a value on human life. And so, it becomes very controversial quite quickly. So, if you use it in -- as a general conversation, there is a cost benefit of PRT that

we can discuss. You know, what are the pros and cons.

But when you say a cost benefit by an economist, it means something that for most part in health and medicine, we don't do cost benefit analyses of health technologies for the exact reason. It's a little bit different in other kinds of large scale engineering projects where there is, you know, different, sort of, theoretical constraints. So I don't know if that answers your question but I didn't say cost benefit because it can be very confusing to different audiences.

DR. FLEGEL: Of course, if you transfuse a platelet and we see a severe sepsis and a patient may die then it's difficult to explain to these patients and the family, we have a technology that would have prevented that but we didn't apply it because the cost efficacy, efficiency wasn't that high. So, one has to consider that from a physician's perspective. And particular also a patient's perspective. We do

have technologies to prevent that and --

DR. CUSTER: You are absolutely right. I do think there was a bit of a challenging scenario because if an inactivated platelet was the only option and that was all that's available and the person lives or dies, that's a very different circumstance than if there is a platelet preparation that's available but it wasn't pathogen inactivated.

DR. FLEGEL: Yeah. All right. If there are no additional questions and we don't questions from the online site then I would conclude this session. There is an announcement by Dr. [Sidi]. Oh, there is one question. All right let's address it.

QUESTIONER: So, it's the same question actually. The question was regarding the cost of pre-splitting in order to meet the (inaudible). You now have to use multiple single volume kits to treat one donation versus using dual storage kits.

DR. FLEGEL: Put the mic on, please.

MR. REEVE: Yeah. There we go. That

gets into a pricing relationship with our vendor in terms of working on the technology. But bottom line is that if you have to use more kits to treat, the cost does go up because you are using more supplies to treat a product, whereas previously, assuming that the pricing is uniform, that each kit is priced the same, theoretically you use more kits to treat one product. It's going to cost you more money. But that's where the relationship between the vendor and the blood center comes in, in terms of, you know, how much you pay for the kit.

DR. FLEGEL: All right. Thank you. I assume there is no additional question at this point. Which then would conclude the session too. We reconvene at 1:55 this afternoon after lunch break. And there is one quick announcement for the shuttle service tonight.

ANNOUNCER: Yeah. Those who are staying in Downtown Silver Spring Courtyard Marriott, the pickup bus in the evening will be available at 5:30 in the building 1 circle out there. And then

also, who pick up the lunch here, if they want to have more space to eat, room number 1406 and 1408, towards the restrooms are available. Those rooms you can use and you can use to have your lunch there. Thank you.

(Recess)

DR. GOODRICH: If I could ask people to start making their way to a seat. We're going to get started here with the afternoon session of the discussions continuing the program from this morning. I'd also like to ask the speakers for this session if you would please come up front, Dr. Benjamin, Dr. Cancelas, and Dr. Razatos. Just a couple of announcements, general announcements upfront, each of the speakers will have 25 minutes in this section. We will take questions at the end of the session after all of the speakers have presented during the panel discussion.

I am just going to introduce the speakers. Their biographies are actually included in the handout that you should have received when you came into the room. So we'll dispense with

that and just get started.

This session is pathogen reduction technologies for whole blood and red blood cells and I'm very pleased to have been asked to moderate this section, as well as to do a presentation in this session. I thank Dr. Atreya and the folks at the FDA for the invitation to this important discussion.

I was posed with a very interesting question by Dr. Atreya and I told him I was going to try to answer it and that is optimal pathogen reduction system for blood safety. Is it a dream? And it's a very good question and I think it's one that's worth answering.

I currently serve as the executive director of the Infectious Disease Research Center at Colorado State University and I'm a professor of Microbiology, Immunology, and Pathology at Colorado State University. So I work for the state of Colorado. I do not represent the state of Colorado. I leave that to our good Governor Hickenlooper and our soon- to-be-governor, Jared

Polis.

So I will, just in terms of disclosures, I have a few things to disclose. I wasn't always at Colorado State University. I am an inventor of pathogen reduction technologies utilizing psoralens and riboflavin. There are patents related to both technologies that have my name on them. I worked in the development of these technologies for nearly 29 years for private industry organizations from almost nearly the beginning of the concepts in this field. I've been the recipient of consulting fees from several organizations that work in this space and that includes Terumo BCT. That is one of the organizations that's represented here on the panel, as well as a developer of these technologies. I do get paid to do that, so I think it's appropriate to disclose it, though I have to say, they ignore most of my advice. I'm compensated for not being listened to.

I am going to express my opinions during this presentation and I'm going to try to be

equally provocative to everyone here. If I fail to provoke you, please come and see me afterwards and I'll see what I can do to get you your money back.

So, an optimal pathogen reduction system for blood safety. Is it a dream? And I said I would try to answer this question. Yes. It is. Very clearly it is, I mean, we're still here 30 years after we started discussing and debating the pros and cons about whether or not we should implement these things routinely, talking about the cost, talking about the decline in in vitro and in vivo clinical behavior. So very clearly the answer is yes, but then when you think about it the answer is also no because these technologies have been implemented. They have been approved here in the United States. They have been approved in various places around the world. They are still in clinical development. The answers are still coming in, so that's not a dream, that's a reality. That's a reality that we're dealing with. Some people might say it's a

nightmare, but it is something that is becoming real in various parts of the world and increasingly so here in the United States.

So having answered the question I could actually just stop right there, but I won't because I bought this new tie and I want it to be a cost effective investment and get some value out of it to do this presentation. So, what I thought I would do is go back in time.

I actually started my work in this field in 1988 and my first venture into this area was working with psoralen compounds. I'll tell you a little bit about that experience in later portion of this talk, but around 2000 I was no longer working with psoralens. That's when the riboflavin technology really came into play. And I was asked at a meeting, AABB meeting here in Washington, D.C., in 2000, so 18 years ago in October, to give a talk about what I saw as issues associated with the new emerging pathogen and activation technologies. And I wrote a four- or five-page document that ended up in an AABB

monograph and you could actually go back and find it because I actually went back and found it.

And it was interesting, I gave a talk at that meeting, which was based on the monograph that I wrote, and I pointed out five things that I thought people had to be aware of as we consider pathogen reduction or pathogen inactivation technologies into the future, five factors. There will be a measurable reduction in protein quality following treatment. Agents may be added to the blood supply, which are not common blood additives or routinely present in the human body. Not all pathogens will be eliminated by the application of these processes. Process control will be essential to assure reproducibility and reliability of these methods. And these processes will add cost.

Now, after I got done giving that talk, Bernie Horowitz came up to me and said, great presentation. I love the way you present information. Are you nuts? And I said, well, Bernie, time will tell. So here we are. Today

we'll be able to tell, was I nuts?

In part I felt compelled, however, at the time to follow through on some advice that my mother gave me many years ago, which was that when people in the secular world approach you with the solution to all of your problems and the perfect answer, the best thing that you could do is cross the street and make sure you still have your wallet. So I thought it was important starting off in this field to lay things out in a very straightforward way. My mother, by the way, turns 83. I'm going to visit her right after this meeting, turns 83 this week and she's still giving me advice. So some things never change.

Dana did a wonderful job describing this issue and I call this light up now and I don't have to go into the details of it because she outlined, I think, perfectly that there are changes that occur to these products and we've known this for quite some time. There are in vitro changes and there are in vivo changes. This is the article that she referenced, "Pathogen

Reduced Platelets for Prevention of Bleeding." This is actually the Cochran Analysis that was done from that data. It was published by Lise Estcourt and several other co-authors not too long ago.

The bottom line, I think, or in the early days we wondered about all of these changes that we were seeing in the in vitro characteristics and we were saying, well, does it really matter? You know, the pH is different, the swirl is different, the extended shape change is different, the HSR is different, the aggregation responses are different, but what does it really mean? And no one knew the answer to that. And I think what's happened over the years is that we have gone into clinical studies, we have generated data, some of that data says there is reduced recovery, there's reduced survival.

As the Cochran Analysis indicated here, those changes clearly indicate a refractoriness in the platelet transfusion increased in these cases. That's not immunological refractoriness, that's

just simply that the count increments aren't as high as you get with an untreated platelet product, but the bottom line has been that despite these differences, these products work. There isn't evidence of increased morbidity and mortality. There isn't increased evidence of acute adverse reactions and there isn't evidence of an increased risk of bleeding.

So, yes, these are not your mother or father's platelets, but they do function. They do work. And I think, importantly, if we get to a point where we could do this with plasma and eventually get to a point where we could do this with red cells, I think we're going to find the same answers. These processes change these products, but the fundamental thing we have to address is do those changes really impact things in a clinically significant way relative to their function in vivo in doing what they're supposed to do. That really is the question we have to answer.

This next one is one of those

provocative slides and I have to tell you my reason for saying this, agents may be added to the blood supply, which are not common blood additives or routinely present in the human body. I think this qualifies.

I was working on the psoralen-based chemistry back in 1988 and after two years we felt we had enough data to come in and have a pre-IND meeting with FDA. And we did. This was with a company called Cryopharm that I was a part of. And in that meeting we went through some of our early data and our proposals for what we planned to do and the next stages of work over the next several years and Joe Fratantoni led that meeting. And after that meeting was over he came up to me, he put his arm around my shoulder, and he said, psoralens? That's going to be a mighty hard row to hoe. And being a young man and getting advice from an older, wiser person who had been there before and done it before, I did what every young man of that age would do, I completely ignored him. And over the next six years I learned what

he was saying firsthand.

There are challenges that are associated with putting agents into blood because of the way that blood products are utilized. I could go on about bis-alkylation chemistry and how these compounds work, but I think one of the interesting comments that I got back from a colleague of mine who was with the NSF in the chemistry division. I showed him this molecule and I said, how would you describe it? And he said, it's a chemical warfare agent, which is tied to a biological glue by virtue of a trigger.

And the issue that we're going to face with putting things like into blood is, will they react to foreign things that are inert? How efficient will that be? Can we quench them with agents like glutathione that we can put into the system to get rid of them? Can we wash them out? How much remains bound and left behind? What are the long term exposure issues to those residuals? This is a question I think that will have to be addressed if we're going to go this route.

Riboflavin doesn't have that issue, but that doesn't mean that it's without issues. I think we heard some of the earlier presentations the issue -- the primary issue associated with the use of this compound is, does it kill enough stuff to be effective? Well, it would be helpful to know what "enough" really is. That's been a difficult question to answer.

We've tried, I think, Steve mentioned in his talk an article that I wrote with Brian and Mike many years ago, a more recent article taking a reflection back on some of this information that was published recently. And I believe there is a new review of this topic that is going to come out in Transfusion. It was authored by Jeff McCullough, Paul Ness, and Harvey Alter. And one thing that I learned over the years with that experience with Joe Fratantoni is when you get three wise people together who have an opinion you should pay attention to it and I think it would be worthwhile to read that article, review that information, and consider it in the context of

what is enough? What do we need to achieve in order to be effective in order to carry out these chemistries?

Not all pathogens will be eliminated by the application of these processes. Now, when I wrote that I wrote it specifically for non-envelope viruses. Knowing what some of the limitations would be with these compounds being able to penetrate the capsid of non-envelope viruses and their ability to show a reduction in infectivity and prevention of disease transmission. There has been some evidence that has been provided that indicates that that effectiveness does translate to cases where transmissions do occur even when the products are treated. We may question the strength of that data, but it's out there.

Interestingly, there's not been in vitro data, that I'm aware of, that indicates that in vitro you can see inactivation of this agent. The riboflavin-based technology has the opposite situation. There's been some data that says that

you can inactivate it in vitro. And this data was generated by the Japanese Red Cross several years ago, but we don't know whether or not that in vitro results translates to a reduction in infectivity in an actual clinical setting and until there's a lot more data and a lot more information available either through hemovigilance or other reporting systems, we may not fully know the answer to that question.

So, I think it's interesting we have one technology that can inactivate things in vitro, but we don't know what the in vivo outcome is and we have one technology that we don't know whether or not it inactivates in vitro, but there appears to be data that indicates that there are transmission events occurring with a non-envelope virus.

There's also the question about what is it that we're trying to do with these technologies in terms of the limit that we're trying to get to? We know that not all pathogens will be eliminated by the application of these processes. So the

question is how effective are we in preventing disease transmission?

And this is a study that was done several years ago, I was a co-author on this work, looking at the ability to inactivate malaria parasites in blood and prevent transfusion transmitted malaria. Over 30 years of working in this field I think this is one of the only, if not the only, article on pathogen reduction technology that actually looked at this question. Can we prevent disease transmission? That's what these technologies were intended to do, but we really haven't answered the question.

Now, in that paper there were two depictions of the data and in looking at outcomes. There was one, what we qualified as a breakthrough transmission, which we assumed was due to the inactivation chemistry not being effective enough to completely eliminate every agent that was present in those products. We looked at allelic matching and then we just looked at days of parasitemia, two consecutive days of parasitemia.

So if you look at this, and I've heard it presented in some forums, as a failure, but if you look at this in terms of what it says that either way, whether you count the allelic matching or not, there is a 70 to 90 percent reduction, which is statistically significant between treated and an untreated product in the prevention of transfusion transmitted malaria.

So what does that mean? Well, if we look at the actual risk of disease transmission based on the yields that have been detected in these locations in Sub-Saharan Africa, that might translate to 168 cases of HIV, 1,400 cases of HBV, 800 cases of HCV, and over 10,500 cases of transfusion- transmitted malaria. If we could reduce those by 70 to 90 percent is that a failure or is it a success? And I think we have to ask that question. That's a big if.

Well, Aaron Tobian is going to look at this question and, I think, provide us with an answer. Aaron has proposed a study, which I think now is registered on Clinicaltrials.gov under the

title "Merit," which will take place in Uganda. It is a collaborative effort between Johns Hopkins University, University of Minnesota, University of Arizona, Colorado State University, Makerera University in Uganda, and the U.S. Army Medical Material Command, and basically it has three aims. We're going to assess the feasibility and sustainability of implementing a whole blood process in a limited resource setting. We're going to conduct a randomized trial to evaluate the safety and efficacy to reduce transfusion transmitted infections, which include HIV, HBV, HCV, HEV, HHVA, bacteria malaria, and complications such as transfusion associated GvHD. These are non-leuko reduced whole blood products that will be studied, over 5,000 products is the number that we came up with in order to reach statistical significance.

Furthermore, we will evaluate the cost and public health impact of transfusion transmitted infections in Uganda with the implications to the value of the Mirasol system to

cover health economics for the region. These two cannot be separated from one another. The question is does the value of reducing these diseases, by whatever measure we determine to be the case, is it offset by the cost that's associated with implementing a technology such as this in this setting? That must be answered.

Process control will be essential to assure reproducibility and reliability of these methods. You've heard about guard bands. So both technologies have these issues, throughput, incoming product specifications, outgoing product specifications, the media for storage of the products, losses and transfers, timing of process steps, record keeping, cost of manufacturer disposables, cost of manufacturer equipment. These are all the practicalities that have to be dealt with with putting these in place.

Now, that has been dealt with to a large degree, although there are still issues as you heard about earlier today with platelets and plasma. Multiply them by 10 when you're dealing

with red blood cells, whether you're using an illumination device or not, the logistical and practical implications of doing that with whole blood or with red cells is a magnitude larger than the issues that we're seeing with platelets today.

How will we do this? I think it's going to take some good old-fashioned Yangtze ingenuity. We're going to move from Yankee ingenuity where these technologies were developed to where they're going to be reduced, I think, practical practice in a very different environment.

This is a product which is being used in China today. It's based on methylene blue. It was CFDA approved in 2010. It received a CE mark in 2009. There are three disposable sets for treating plasma with methylene blue and the cost of those sets is 30 yuan, 36 yuan, and 45 yuan. For perspective 1 U.S. dollar is equal to 7 Chinese yuan. So we're looking at $4 to $5 for these sets, okay? That device will treat 70 units at a time. I've been in blood centers in Shanghai that have 5 of these devices working 5 days a

week, 5 times a day, they're producing between 400- and 600,000 units of methylene blue treated plasma every year. Swap out the bulbs in this and you've got a whole blood treatment system.

This is the type of environment that they're making these products in. There's no difference between the setting of the manufacturers that you see here and what I know from manufacturers in the United States or Europe. So these are not low-cost/low-quality, but low-cost/high-quality products.

There's also some work coming out of China that's describing new systems that utilize a riboflavin and UV in this case approach to inactivate pathogens in a flow system to increase throughput, to decrease time of treatment per unit. There's no reason why these systems couldn't also be adopted for use in whole blood treatment. The technology is there. It might be the psychology that prevents us.

What do I mean by that? Well, these processes will add cost. I saw this article in

the Wall Street Journal, we can't afford the drugs that could cure cancer, the war on cancer, we can't afford it. I sent this to a colleague of mine at Abbott and he wrote back and said, eh, we've heard that about every drug we've ever developed over the last 30 years, but that hasn't stopped them from selling them. And I think the reality is that we find a way to make it happen when it matters. When it makes a difference, we find a way despite what the cost may be or we find ways to make it less expensive. So I think that eventually we will find a way to make this happen.

That's my cartoon for what I think the future holds. It doesn't mean we've done it, it means we can do it. Will we do it? That's a different question.

How do you make this happen? An example, I think, is working with NGOs, working with other groups to get implementation. After the AIM study there was work that was done with the government of Ghana to implement the technology for treating whole blood and routine.

That data was generated under a system that was put in place by the AABB international group, working in Ghana to establish hemovigilance. That data has not been presented yet. I actually had an opportunity to get a sneak peak of what's in there. It's better than we could have hoped for and I think as a result of seeing the results from that work, I believe, I'm not 100 percent certain on this, I believe that the government has now decided to implement this technology and routine on their nickel. So they're finding a way to afford it because it has value that is of benefit.

Enough about the past, what does the future hold? So these are my predictions. I did check the calendar. This room is open 18 years from now on this date. So I'm willing to come back if there's anyone left and tell you how I did on these predictions.

So, I think PRT treatment of blood products will become a universal process, but I think adoption is going to continue to be slower absent in high income index nations. The

companies that are out there right now are trying to sell the product to people who can't afford it and I mean the United States, Canada, Germany, France, and Japan. What they need to be doing is focusing on developing a product that they could sell to the people who need it because if we solve that problem for them, we will solve the problem for everyone.

These technologies will be adopted to address vulnerable populations initially and broader populations eventually. I think where there's more risk that exists, pediatric patients and chronically transfused patients, there will be more of a driver to use these types of products. I think the situation with pediatric patients is quite interesting because if you could take a unit of blood and fractionate it into four or five transfusion doses, you've reduced the cost per transfusion in that setting by four to five fold. It takes on a different dynamic in terms of cost-benefit, cost-effectiveness analysis.

New providers are going to drive

innovation in the field. No disrespect to my colleagues who are in the room today, but I believe there are going to be new providers, there are going to be new developers who are really going to advance this to another stage, bring this forward into a format that people can use more broadly and globally for products, and finally new disease with the transfusion transmission throughout will emerge. It's nature. It's going to happen. I think as a result of that we'll probably continue the debate, we'll wonder what we should do about, and we'll hold more workshops. I'm pretty sure I'm going to get that one correct.

So, I have a little story to tell because I've been provocative as I said and I want to point something out also in myself, I have to look at this, it has to do with bias. There's a story about a congregation that was replacing its minister who had been the minister there for many years and it was an elderly congregation. And they hired as a replacement a young female minister and, of course, there were a lot of eyes

that were rolling and concerns that existed among this group of people where that was unusual.

And so, the women in the group said to their husbands, why don't you take this young woman out and take her fishing and, you know, get to know her, you may like her. And so, they did and they go out and she casts out a line and immediately pulls out a bass and says, wow, what a great trout. It's incredible. I've never seen a trout like this before. And the men look at each other and they say, uh, you know, just roll their eyes.

And then a storm comes up and the boat capsizes. And this young minister gets out of the boat, walks across the water, pulls every one of these men out of the water, brings them to shore, and saves their lives.

Sunday comes along following this. They're all standing around outside the church and the young minister comes in and smiles and waves at them. One gentleman turns to the other and says can you believe what happened last week? Can

you believe that? And the other one says, yeah, I know. She couldn't tell the difference between a bass and a trout.

Which the story -- the moral of that story is that if you look for defects, if you look for problems and you have a bias, you will find them, but in the process you're going to miss the miracle. And I think there have been some miraculous things which have been done.

Dr. Atreya's question, I think, was, has this been a success or a failure? But he's too much of a gentleman and a scholar to ask me that directly. I would say that success comes in different measures. It's a matter of perspective. If we thought at the beginning that we had the perfect solution to anything and everything, then it's a failure. If we thought we were going to make a difference in some people's lives and these are some young sickle cell patients in Ghana, I think it's an incredible miracle of what has happened and what will continue to happen in this field.

Now, my departure from this field was somewhat abrupt and unexpected and I never had a chance publicly to thank the people who supported the work that I did and the things that I did and my colleagues did. And the things that have developed in this field would not have been possible without the help and support of these organizations, which includes a congressionally designated medical research program or P peer-reviewed medical research program, BARDA, U.S. Army Medical Command, and folks that are associated with these various groups. They made these things possible and I believe that they will result in making a difference in the way blood is handled and treated in the future to provide safe and effective products to patients around the world.

So I'm going to end there and I want to introduce Dr. Richard Benjamin from Cerus Corporation to talk to us about, I'll get your title here, Richard, "Clinical Experience with Pathogen Reduction for Red Blood Cells Completing

the Triad." Thank you.

DR. BENJAMIN: Well, Ray, you're a hard man to follow and thank you for expressing your opinions. I can tell you that I'm not going to be half as entertaining. I'm going to try and stick to the facts and the data, but yeah, I haven't been in the industry for 29 years.

Let me start -- I want to talk about pathogen activation for red cells and our experience with that in Cerus. I might -- disclaimers are I am the chief medical officer of Cerus Corporation and I own stock in Cerus Corporation. I need to start off by recognizing the funding that we've received from BARDA from the biomedical advanced research and development authority. Without their support, we really couldn't be doing this important work that we are doing.

So, an ideal state, we would all like to take fresh wholesome blood from a donor and transfuse it to patients that need it, when they need it, and be a lifesaving therapy. One of the

problems we have is that a lot of patients, the majority of patients, don't actually need whole blood, they need the components and we have constraints on when to make those components, et al., is to make platelets and fresh frozen plasma and restore them in different ways and so this all impacts the concept of how we do pathogen inactivation of whole blood. The other big problem, of course, with all blood donations from donors is that we get everything else that comes with the blood, including the leukocytes and the plasma, which often we don't need in the transfusion and also the commensal and pathogenic microbes of the donor.

We've heard a lot of focus on the pathogenic microbes. We're becoming increasingly aware of the commensal microbes that people carry and we really have very little understanding of the impact of those on our patients at all. We assume it's zero. We've made that mistake too often making those assumptions. We will learn over time. And then let's not forget immerging

pathogens. We all think of dengue, Zika, or the possibility of yellow fever, but remember that HBV, HIV, HCV, West Nile, Chagas, Zika were all emerging viruses at one point in time and the next one is going to come. It's around the corner. We are not very good at predicting. If we look at the AABB's list of the 60 somewhat at-risk viruses back from 2009, I don't believe Zika was even on that list. So surprises, that's what we are going to get.

So we really do, in my mind, need pathogen inactivation for all three labile products. Whether that's through whole blood and separation of components or through PI of each individual system, we need to protect ourselves against emerging pathogens. That is part of emergency preparedness.

We also need to protect against residual risks that we know about. Today we have protection about Babesia, CMV, graft versus host disease, that's incomplete because we're selective about how we use those technologies. We like to

protect ourselves and that leaves patients susceptible. For graft versus host disease, we know that half the patients that get graft versus host disease didn't have or don't have any risk factors and, you know, we're -- did not receive irradiated blood products because they did not fall within the categories that require them.

So the idea of a universal versus a selective approach is very attractive. We also have things like malaria and dengue and chikungunya where we rely on travel deferrals and we don't have any tests and so there's a window of risk there.

We also have an opportunity with pathogen reduction to improve the products. We know that irradiated blood products have high levels of potassium. They have increased hemolysis. It would be nice to get rid of those issues.

We also have an opportunity to remove the residual plasma and reduce risk of things like allergic reactions, anaphylaxis, and even possibly

TRALI. And, of course, the overall societal benefits of avoiding future viral market tests and reassessing current tests are there, relaxing donor, deferral criteria, and getting rid of irradiators, which are basically terrorist threats as they stand. So lots of good reasons for universal pathogen reduction.

So, Cerus's solution has been the INTERCEPT blood system. We target nucleic acids to prevent replication of pathogens and we've specifically avoided systems that give rise to reactive oxygen species. We do that because reactive oxygen causes direct damage. For red cells, in particular, it causes hemolysis. So we avoid UVB light for that specific reason of the reactive oxygen species.

We also recognize that there has to be a balance between optimizing pathogen inactivation and also considering functional activity of the red cells, platelets, and plasma. Having said that, in our mind the pathogen reduction is paramount. If you haven't got effective at least

four lugs pathogen reduction, you haven't got a pathogen reduction system and it has to be broad-spectrum and a pathogen reduction system that doesn't have broad spectrum pathogen reduction capability, is not a pathogen reduction system worth having and I think it's a false sense of security and so probably not worth doing.

So, in order to solve these problems of optimized pathogen inactivation and conserving function, Cerus has developed two separate technologies. For platelets and plasma we have the amotosalen UVA light system and that today is the only platelet system that has proven safety, efficacy, and quality to meet the FDA standards for use in the U.S. It's also the only system that has met the safety and performance criteria of Swiss Medic for use in Switzerland. It's also the only system that has met the safety and performance and quality criteria for use through ANSM for France and Health Canada in Canada.

CE mark is important, but it's just a mark that your product is safe. It tells you

nothing about efficacy. These other approvals really look to the efficacy and quality of your product.

INTERCEPT platelets are already in universal use in high-income countries like Switzerland and France and Belgium and increasingly in the U.S. Today the majority of the platelets at the NIH, at the Walter Reed Medical Center, at the Mayo Clinics, at Yale, and many other institutions are INTERCEPT treated. INTERCEPT blood system for platelets is the first and only system to be associated with a significant decline in the reported septic transfusion reaction rates on a national basis in France, Switzerland, and in Belgium. So we see that as a success.

For red cells, we're developing the S-303 or amustaline system, a compound that also targets nucleic acids. Amustaline has three components. It has an alkylating arm that does crosslink or form (inaudible) to DNA and RNA. It has an anchor acridine function that targets. So

it is targeted. And it has a linker that breaks down quite rapidly in neutral pH. If you look at the degradation kinetics, you can see here it's a two-phase degradation and that within 20 to 24 hours and a single wash it is below the limit of quantitation in the blood product.

We have performed already the most extensive toxicology testing possible, principally with the INTERCEPT treated red cells themselves, but also with the breakdown products that are left from the compound such as S-300 or acridine. We've done acute toxicity, sub-chronic toxicity, chronic toxicity studies. We've done reproductive toxicity. We've done neonatal, genotoxicity, carcinogenicity, and the treated red cells and the breakdown products of our compounds have met all the criteria for safety for all patient populations including children, adults, neonates. So we are confident that our blood products are safe. We are also confident that they effective. We've done an extensive list of in vitro inactivation steps and shown robust inactivation

across a broad spectrum of pathogens.

Very importantly, we've looked at T cells and shown that we get very effective inactivation of T cells and as I mentioned earlier today, the biggest concern actually is that irradiation is not particularly effective at inhibiting T cells, there is residual activity left of the radiation that we don't see when we treat with our own compound. I was surprised, actually, when I went back and realized how many of our blood products today are irradiated.

The AABB report said 20.6 percent of all red cells and 58 percent of all pediatric red cells are being irradiated today. That's selective irradiation and that does harm red cells. You get higher levels of hemolysis, plasma hemoglobin, and potassium and a shortened shelf life with irradiation. So I do see a major advantage of the INTERCEPT red cell system to actually provide a better product than an irradiated product for these patients and also a safer product because it would not be selective,

it would be universal pathogen reduction.

So one of the issues that arose with an earlier version of the system, was the generation of antibodies to the acridine molecule on red cells and it did lead to the halt of clinical trials back in 2002 or '03. And so we do know that natural reactivity occurs. In that case, the antibodies eventually prove to be non-clinically significant, though negative in an MMA assay, they were a very low titer. There were not of an isotype that would cause a problem.

So we have actually developed an assay for acridine antibodies and we did screen 10,721 patients in Germany and almost 1,000 thalassemia and sickle cell patients across Europe and the U.S.A. for natural antibodies that had never been exposed to S-303 red cells and we actually picked up 17 patients that had natural antibodies, most of them, 14, were inhabitable with S-300 or acridine. Turns out that acridine actually used to be very common in the environment. It used to be part of clothing dyes and it's a part of some

antiseptic solutions that are currently even still on the market today. So it is an antigen that it's in the environment.

When we looked at the 17 re-activities, 13 of them were IgGs, but they were not IgG1 or 3s, which really caused some problems with hemolysis. A couple were IgM. Most, in fact, were not reactive with the new -- the current system of treatment, so we did change our treatment system. We did actively look to reduce the amount of acridine or S-300 on the red cell surface and we actually show that most of these natural antibodies did not -- do not react -- did not react with our current system of treatment, the all low titer, and we've assessed that these are non-clinically significant, and we fully expect to see such antibodies in our clinical trials and down the road and would treat them as non-clinically significant. We will investigate them fully as they occur and demonstrate this clinical significance.

Before I go on to our clinical trials

that we have done with packed red cells, I want to say a few words about a whole blood system. We are working on a whole blood system, specifically for use in austere environments. It's a different set of chemistries. A different ratio of chemicals than we use in packed red cells. Today it would be a single bag -- actually a two-bag system. You sterile dock your whole blood unit onto another bag, you add the compounds GSH and S-303, you have a similar 24-hour room temperature hold and you store for up to 7 days and transfuse. This system has not been optimized for platelets and plasma and we are working, in fact, on looking at optimizing the system for the co- components, but at this point we are planning on a clinical trial in collaboration with the Swiss Red Cross in Africa to look at austere environment use.

So, what about the packed red cells, pathogen reduced packed red cells? This is our clinical development program. With this redesigned system of pathogen reduction, we have gone through two recovery and life span studies in

normal volunteers, and I think, Dr. Cancelas, will be talking more about that work after me today. We successfully passed those milestones.

We went in Europe, performed a study called STARS in Germany where we randomized 51 cardiac surgery patients to receive test or control red cells. We went on to a thalassemia study in Turkey and Italy for 81 patients, and I will describe the outcome of that study. We received funding in the U.S. from BARDA and we have a study called RediS that's now ongoing. I'll say a few words about that. And we have recently begun enrolling patients on a large cardiovascular surgery study called Recipe. We have plans for a chronic transfusion study or two chronic transfusion studies. It's not yet clear whether that will be pre-PMA or post-PMA or a combination of the two and we do need to have further discussions with the agency with what information we will have to have when we submit our PMA.

So, Dr. Cancelas, will show more data

about the recovery and survival study performed partially -- half in his lab did show that we did meet all of the FDA requirements for recovery for red cells. The area under the curve for lifespan were not different between the two, although some small differences were seen in the median lifespan in these studies.

The STARS study, 51 complex cardiovascular surgery study in Germany, essentially this was really designed to look for CE marking where you have to demonstrate the safety and performance of your device because this is a device in Europe and so our primary endpoint here was really looking at the hemoglobin content of the red cell units. Could we meet the specifications for a high-quality product consistently and could we meet the EDQM, the European guidelines, for things like hemoglobin content, hematocrit, and hemolysis?

Our clinical endpoints were secondary and exploratory, so we looked at renal insufficiency, hepatic insufficiency, and a

six-minute walk test as a measure of oxygen carrying capacity. Our primary endpoint was, indeed, the hemoglobin content and we showed that we were non-inferior between test and control. I think the mean was, I think, 2.1 grams difference that were basically lost during the processing. End of storage hemolysis shown here was actually less in the test than the control. This is with 35 day storage. And, in fact, a lot of the other in vitro parameters not shown were better in the test than the control including things like potassium levels. So, we know we have a robust system.

In terms of clinical outcome, we saw no difference in renal insufficiency and hepatic insufficiency, no difference in the six-minute walk test, at first ambulation or at day 13 or discharge. So we met those endpoints. Adverse events were equivalent between the two and we saw no antibodies to the S-303 treated red cells. This paper has been published by Brixner, et al., in Transfusion this year.

We then went on to a large clinical phase 3 study in Italy and Turkey where we approached thalassemia patients, transfusion dependent thalassemia patients. These patients receive red cell transfusions every two to three weeks for the rest of their lives. In our study, this was a randomized crossover study, they received six cycles of test and six cycles of control.

The first two transfusions were wash in transfusions and the next four were the efficacy evaluation transfusions. We included children. Our primary outcome was hemoglobin use. The biggest risk to these patients is iron overload and we wanted to make sure that we're not going to use more red cells because they were treated. So hemoglobin use as grams of hemoglobin, the kilogram body weight per day, and this was a non-inferiority study. We also looked at adverse events and for antibodies to S-303 red cells.

Since thalassemia, for those of you not familiar, this congenital disease of the beta

chain of hemoglobin, patients have ineffective erythropoiesis and expansion of the bone marrows into hematopoiesis in the spleen. They have growth failure, splenomegaly, bony abnormalities. Transfusion itself, in a regular transfusion program, can make their life normal, except they get iron overloaded and therefore they go into iron chelation therapy and we have patients out of Izmir, Turkey who basically lead normal lives as long as they get transfused on a regular basis.

What the problem is, infectious disease. In the '90s, when chelators came in that was a miracle for these patients, but then they all got hepatitis C. So, they are highly susceptible to anything that's going through the blood system and ultimately would be a great population for pathogen inactivated red cells.

So, this study finished end of last year. We are busy submitting -- have submitted the paper for publication. We enrolled 81 patients, 67 in Turkey and 14 in 2 sites in Italy. The mean age was 26 years. We had 15 children,

less than 18 years old, half female, half male, but half of them had been splenectomized and that dramatically affected the amount of red cell support they needed.

The Italian patients were held to a higher baseline hemoglobin, 10.2 versus 9.3 in Turkey. In these patients you aim to keep their hemoglobin between 9 and 10.5. The Italians were holding at the high-end and the Turkish were holding at the low-end. And that, too, is reflected in the amount of hemoglobin of red cell transfusions they got. Five Turkish patients had preexisting red cell alloantibodies and, interestingly enough, in Turkey most of these patients simply got ABO compatible red cells. They were not phenotypically matched, whereas in Italy they were phenotypically matched generally.

They went through six cycles of tests, six cycles of control, transfusion interval on average was about 19.5 days, not different. The red cells given were just eight to nine days old, not different, and the total components each

patient received on average 12.5 tests and 12.5 control red cells. There was a 13 gram difference in the total amount of hemoglobin between the two arms, which very accurately reflects the amount of hemoglobin lost between the two arms, which is about a gram out of a 50 gram unit.

We had very good compliance. We only had 11 of protocol red cells given to 2 test, three control red cells -- patients. Primary efficacy endpoint was hemoglobin consumption. It was met robustly in both the intention to treat and the per protocol population, difference being.001 and.002 where our margin was 0.17, so very robustly met the consumption endpoint. Safety endpoints, we saw no antibodies to S-303 red cells, no red cell alloantibodies, all other adverse events were equal between the two arms. In severity, in relationship, transfusion reactions were the same, no difference. The INTERCEPT red cells were non-inferior to conventional red cells at chronic transfusion support of the thalassemia patients. The safety

profile was comparable and no antibodies emerged.

I have three more slides. Please, sit down. Please sit down. Thank you.

We have two studies going on in Europe. The RediS study is going on in Puerto Rico and in -- three sites in Puerto Rico, three sites on the mainland and it's designed as a Zika high-risk area transfusion. We have enrolled patients robustly. We had a hurricane halfway between our enrollment, stopped enrollment for a year, but we have now doubled the number of patients exposed to our red cells in the study worldwide. We're looking at hemoglobin increment as the primary endpoint. The Recipe study was just opened for enrollment. We will enroll 600 patients to receive test and control red cells and we will look at kidney injury as a primary endpoint.

In conclusion, pathogen activation for labile blood products is becoming a reality to protect against emerging pathogens. We do believe our product will improve the components. We believe that we will be able to avoid viral market

test in the future and (inaudible) when we have all three components available and gamma radiation should be a thing of the past.

And I do want to finally acknowledge BARTA for their continued support, for the many investigators that have contributed to the program and specifically Dr. Larry Corash, Nita Mufti, and Lloyd Ison at Cerus and the whole Cerus staff for their continued efforts. Thank you very much.

DR. GOODRICH: Sorry about that, Richard. I didn't have your slides, at least the ones you presented, so I wasn't certain how many more you had to go. Next time I'll have Simone come up and stand here.

I do want to introduce, Dr. Anna Razatos, who will be talking to us about the state of the PRT for whole blood from Terumo BCT.

DR. RAZATAS: Thank you, Ray. I'd also like to thank the FDA and the organizers of this meeting for inviting Terumo BCT and giving us an opportunity to provide an update on pathogen reduction of whole blood.

So, disclaimers, I am an employee of Terumo BCT. A reminder to everyone that the Mirasol pathogen reduction technology system is not approved for use in the United States. It is available under CE mark, as well as country specific regulatory approvals for other world areas and at the end I'll talk about some long-term projects that Terumo BCT is looking into, but with all research and development projects, things rarely go as planned, so.

I'll be focusing on two major areas. First, discussing Mirasol treated whole blood for transfusion. I'll go over the AIMS study and some results from the AIMS clinical study in Ghana, which actually, Ray, also touched upon and then the continued use of the Mirasol system in Ghana to treat whole blood for transfusion, which was supported by a grant from the Japan International Cooperation Agency or JICA. And then also we're very excited to support Dr. Tobian at Johns Hopkins who is doing a study looking at the sustainability of using the Mirasol pathogen

reduction system to treat whole blood in an austere environment. And that also is supported by a grant from the U.S. Department of Defense.

And then I'll switch gears and discuss components derived from Mirasol treated whole blood and touch upon the PRAISE clinical study in the U.S., which is also supported by the U.S. Department of Defense, as well as a very exciting investigator initiated study that's being carried out in Russia by Dr. Trackman.

So, the Mirasol pathogen reduction technology system is based on having one device to treat all blood products. So from an operations and a cost of training perspective, our vision is to have one device that is capable of meeting all the blood center needs and can treat all those products. It is based on riboflavin, which is vitamin B2, which is non- toxic and for that reason there's no chemical removal step. There's no washing. There's no waiting. Actually, products are available to transfuse immediately after treatment and I think we can all agree that

pathogen reduction is a proactive rather than a reactive approach to blood safety.

So currently available under CE mark are three protocols. So there's pathogen reduction of whole blood for transfusion of platelets. In Europe it's for apheresis and whole blood derived platelets and also plasma. Again, all of these products are pathogen reduced on one device using the same vitamin B2 or riboflavin package and so at the end you have these three products that are ready to transfuse.

Just a reminder that the Mirasol system is based on riboflavin, which is added to the blood product and then the combination is exposed to UV light. Riboflavin interacts with RNA DNA and the UV causes photo-activation, which causes irreversible damage to the DNA, which then prevents the replication of viruses, bacteria, and parasites, as well as inactivating white blood cells.

So moving on to the clinical studies. So the African investigation of the Mirasol

system, which Ray introduced or the AIMS, was a clinical study in Ghana and it was the first and only clinical study to demonstrate that PRT can effectively reduce the incidents of transfusion transmitted infection of a blood born pathogen. So it was carried out at a teaching hospital in Kumasi in collaboration with the National Blood Service of Ghana. It was perspective, randomized, double-blind controlled, single center trial. The patient population was limited to adult patients with blood group O+ who were anticipated to require up to two whole blood transfusions within three days following randomization and again, so the endpoint was to look at reduction of incidents of transfusion transmitted malaria and specifically looking at non-parasitemic recipients who received parasitemic whole blood. So the test unit was Mirasol treated non-leuko reduced whole blood and the control arm was, obviously, untreated non- leuko reduced whole blood and both products were controlled for volume. So it was the same volume for each of these products.

So this is a reproduction of the data that was published in Lancet and so if you look on the right-hand side in the top panel, what you'll see is the test versus control arm, so untreated whole blood compared to treated whole blood and then it's plotted by on the Y-axis parasite load. And so the top panel is transfusion transmitted malaria, which is in the solid circles and this is confirmed by allelic matching.

So in that dataset, there were actually in this study, over 200 patients were enrolled, but there were 65 non- parasitemic patients who were exposed to parasitemic blood, 28 received Mirasol treated whole blood, and 37 received untreated whole blood. And so in the untreated arm there was an incidence of TTM of 22 percent and in the Mirasol treated arm the incidence of TTM was 4 percent. So as, Ray, stated this is a successful study. The primary endpoint was met and there's a statistically significant reduction in transfusion transmitted malaria in this study population.

I do want to point out the one transfusion- transmitted malaria case is a reminder that no single pathogen reduction technology or system is going to eliminate all the risk, you know, for all pathogens under every circumstance. We know that there was one case, confirmed case, of transfusion-transmitted hepatitis E in Europe for INTERCEPT treated products and so, you know, even vaccines aren't 100 percent effective. But, again, it's a success story for the percent decrease in transfusion transmitted malaria and as, Ray, pointed out the children or the patients that, you know, weren't infected during the course of this study.

Secondary endpoint analysis was looking at the efficacy of Mirasol -- of RBC's derived for Mirasole treated whole blood and in this case we saw no difference between Mirasol treated RBC's and untreated RBC's in terms of total hemoglobin over the 28 days or 30 days post-transfusion.

This was also an opportunity to collect safety data. So there were 24 transfusion

associated adverse events reported in 223 patients. There was an incidence rate of transfusion associated adverse events of 8 percent in the Mirasol treated arm and 13 percent in the untreated arm. So there was no statistically significant difference between test and control. There was a lower incidence rate in Mirasol, but again this didn't reach significance. And just a reminder this is non-leuko reduced whole blood and we know that Mirasol inactivates white blood cells. So there might be a slight decrease in reactions in this study due to the fact that we're inactivating those white blood cells.

We are seeing continued use of the Mirasol system in Ghana. So JICA supported a grant to allow continued use of the Mirasol system in Ghana, but also to establish an implement, a national hemovigilant system and right now we're starting with two teaching hospitals. The original hospital in Kumasi, which was responsible for the AIMS study and then now we've also added the teaching hospital in Accra and you can see

that these two hospitals transfuse between 20 and 35 whole blood units per year.

So the concept for this project was to train the trainers and empower the local hospitals there to sustain a hemovigilant system. So it's really coming in, building the hemovigilant system, training the people responsible for the system so that when the project ends that there's a self- perpetuating hemovigilant system. So first and foremost was to implement routine use of Mirasol to treat whole blood, which really supports a safe and sustainable blood supply and then again implementing this routine use, hemovigilant system, which overall just having the education and the awareness to improve blood transfusion practices. So there was a centralized data base for these two hospitals to upload data and there was dedicated and trained staff that were responsible for the data entry and again this is safety data. So they're uploading adverse transfusion reaction data and then the project has actually ended.

So it was a two-year project. The project has ended and, as Ray said, we're looking forward to the principle investigators to publish this data. But I will say even with the completion of this project, the hemovigilant system is ongoing. It is self-sustainable now. The expectation is that the hospitals will continue to upload data and then we have gotten confirmation from the Ministry of Health in Ghana that they're committed to continuing use of Mirasol in this country.

So we are also excited to be supporting Johns Hopkins and Makerera University in Uganda as they are also working on a DOD-funded project to evaluate the reproducibility and sustainability of the Mirasol PRT system in austere environments. As Ray described there is three aims.

The first aim is a randomized clinical trial. So this is a second opportunity to demonstrate the efficacy of the Mirasol PRT system to reduce transfusion-transmitted infections to whole blood and then in addition to that there

will be an evaluation of cost and the impact of the Mirasol PRT system to public health in Uganda and hopefully some of that can be translated to other world areas. And then again, this is looking from a military lens. So it's the sustainability of implementing a whole blood PRT system in a limited resource or an austere environment.

The goal is to reach 1,000 transfusions of Mirasol treated non-leuko reduced whole blood compared to 1000 transfusions of standard issue non-leuko reduced whole blood. And this will be a randomized, double-blind controlled, single center study that will be executed, actually, in the capital of Uganda in Kampala.

So whole blood for transfusion in the U.S. Thanks to the efforts of Dr. Cap, who I believe is here today, Dr. Spinella, Dr. Holcomb, Dr. Yazer, we're seeing an increased utilization of whole blood for transfusion in the U.S. and specifically for trauma and massive bleeding.

So in 2014, Dr. Yazer at Pittsburgh

started the, I think, the first low titer group O whole blood transfusion protocol in the U.S. and so you fast-forward to 2018 and there's at least 19 leading trauma centers that are transfusing whole blood and some of those are actually putting whole blood into the pre-hospital setting such as ambulances and helicopters. And so Terumo BCT is evaluating the opportunity for Mirasol treated whole blood in the U.S. I will say that as a mother of a 16-year-old who had his first car accident two weeks after he got his driver's license, I would be very excited to see Mirasol treated whole blood on ambulances in the Denver metro area, anywhere in the U.S. Would be great, but let's start with Denver and then we can move beyond that.

So components for Mirasol treated whole blood. So the future vision, the big picture for Terumo BCT is really automating blood safety. So it's streamlining operations and also decreasing cost with one device to treat all products and so the vision is that you would have any product

coming into the system, whole blood, platelets, red blood cells, plasma, and you would put it through the next generation illuminator.

So as our previous speaker said, you know, it's okay to treat one unit at a time, but when really talking about red blood cells and whole blood, we need to think bigger and it needs to be a high throughput device. And so that's something that we're working on right now, is what's that next generation high throughput device, but you put it through this device, so it's pathogen reduced and then in the case of whole blood you would either use manual or automated methods to separate the whole blood and at the end of the day you have pathogen reduced inventory of all of your blood products.

So outside of the U.S., I would say in the last seven or eight years, we've seen a move towards whole blood derived platelets. And so, I think, Dana Devine, with your leadership at Canadian Blood Services they implemented buffy coat platelets in Canada and, I believe last I

saw, 85 percent of the platelets transfused in Canada are buffy coat platelets. And so I personally believe that this is a trend that's going to continue.

We're going to continue to see more utilization of whole blood derived platelets and I think what may tip the U.S. in that direction is when you talk to blood centers one of the primary issues is apheresis platelets donors. They're an aging donor population and so some of those platelet donors are becoming patients and so as we're seeing less and less apheresis platelet donors the demand for platelets is so far staying steady or increasing. So there may be a time when we have to -- everyone's going to be moving more to whole blood derived platelets and so I think this is exciting to think that you take a whole blood unit, you PRT treat it, and then you have a choice. You can either transfuse it as whole blood or you can make it into components.

The first step towards this pathway for Terumo BCT is the PRAISE clinical trial. And so

this is a trial to evaluate the efficacy of RBCs derived from Mirasol treated whole blood compared to conventional RBCs and it is a non- inferiority study looking at percent survival of RBCs derived from Mirasol treated whole blood and it is in chronic transfusion patients. Perspective multicenter randomized crossover trial, we started this study in April of 2018. The test arm is leuko reduced RBCs from Mirasol whole blood, so the whole blood is Mirasol treated, separated, and then the red blood cells are leuko reduced and then that's the test arm -- sorry, and the control arm is leuko reduced RBCs either from apheresis or whole blood derived.

I will say that we just recently voluntarily suspended the PRAISE clinical trial and that's specifically to address blood supply challenges that we've encountered while trying to meet the transfusion requirement needs of the patients. So there's no health risk to the patients. It was really -- the patient population for this study is chronically transfused

thalassemia patients who required cross-matched RBC products. And so we are having logistic issues having a cross-matched Mirasol treated product available for a patient who's enrolled in the study at the time of transfusion. And so we're taking a pause to try to figure out the logistics and the blood supplier issues.

So one final study, we are very excited to be working with Dr. Trackman, I should say supporting Dr. Trackman. This is an investigator initiated study. Dr. Trackman has started a study looking at the clinical experience of RBCs derived from Mirasol treated whole blood. He works at a pediatric hematology, oncology, and immunology hospital in Russia.

So the first phase of this study was in vitro validation. So it was an in vitro laboratory study looking at the quality of RBCs derived from Mirasol treated whole blood. He looked at whole blood from 50 healthy donors that were leuko reduced bifiltration after collection and then he took 25 of those RBCs, separated them

into whole blood, and stirred them in SAGM and gamma irradiated the RBCs and then the test arm was 25 RBCs separated from Mirasol treated whole blood and again stored in SAGM.

So he looked at a whole panel of assays. I'm just presenting today potassium and percent hemolysis. So for the majority of assays we didn't see a difference between test and control. So for potassium, for example, there was no difference between the RBCs Mirasol treated red blood cells and the controlled red blood cells. For percent hemolysis, Dr. Trackman did observe higher -- a few units that were higher than the.8 percent hemolysis limit in Europe on day 21. And so for that reason he limited red blood cell shelf life to 14 days. I will point out that for the PRAISE study we did not see hemolysis for Mirasol treated RBCs stored in AS3 and so for the PRAISE study we're storing red blood cells out to 21 days.

So moving on from the laboratory study, Dr. Trackman looked now into clinical study where

he is transfusing these Mirasol treated red blood cells and so this was a formal clinical study, protocol approved by the Russian authorities and he enrolled 70 patients, 35 patients received one transfusion of the control gamma rated red blood cell and 35 patients received one transfusion of the RBC, which was Mirasol treated. And so you'll see this actually was a pediatric hospital and so all the patients were children or pediatrics with malignant disease.

So this is just a snapshot of the preliminary results and so what you'll see on the right hand side is that there was no difference between the treated RBCs and Mirasol treated RBCs in terms of corrected hemoglobin dose and also RBC age and that on the right are the study results, so looking at hemoglobin increment, hematocrit increment, and period between transfusion reported here in terms of days and there was no statistically significant difference between those measures, between Mirasol treated RBCs and untreated RBCs.

I will also say that we received the safety data and there's no difference in reported reactions between the Mirasol treated and untreated red blood cells. And we're very excited, Dr. Trackman plans to publish this data soon, so we're looking forward to his publication.

So finally, Terumo BCT believes every patient, everywhere in the world deserves access to a safe blood supply and our contribution is using automation and innovation to try to make that a reality. Thank you.

DR. GOODRICH: Okay we have a break scheduled for right now, I believe. We're a little bit behind, not too much, but we'll regather here at 3:25 to hear from Dr. Cancelas.

(Recess)

DR. GOODRICH: Okay, if I could ask everyone to please take their seats. We're going to restart here. We have Dr. Cancelas' presentation and then we also have the panel discussion. And if our former speakers would like to join us up front, they're more than welcome to

do that, or certainly will join us during the panel discussion.

So our next speaker this afternoon, our final speaker for the day, I believe, yes, is Dr. Jose Cancelas from Hoxworth Blood Center, University of Cincinnati. Jose is going to talk to us about PRT of red cell products, the impact on biochemical, and viability parameters in humans.

DR. CANCELAS: Thank you, Ray. I want to thank the organizers for inviting me. I'm really honored for being here. I mean, there are much smarter people in the audience that they could be given probably much better talks than myself. So I'm going to give my view based on my firsthand experience along with many collaborators that have worked with us in Cincinnati.

So I'm going to tell you about some of the studies we have done. I'm going to tell you only about the studies that we have done in the last few years, not the many more years ago. So we are starting with pathogen reduction technology

in red cells.

Well, in 2000, so (inaudible) in late 1990s and I started myself in 2002. So we have seen a lot of things, saw many problems, and this is a thing about how to troubleshoot issues. The fact that today we are here having a workshop, a public workshop, tells you that things have improved a lot.

Just to give you an example, 10 years ago some very important people in transfusion medicine told me, Jose, you are not very smart because there will be no pathogen reductions in the United States while we're alive. So I'm very pleased to hear today that that's not the situation. I think the concept is right. It's true that the technology has to improve, no question. I think we are not there yet. We are close, but not there yet.

So now the question is how we can really modify the parameters? How we can retune? I think we need to understand more about technologies, but also we need to understand more

about biology. I'm am a physician and scientist. Always when I try to make decisions I'm based on data, especially biological data. If there's no biological data that can be clinically relevant I'm not very happy. So I'm going to tell you about (inaudible) today and you judge it by yourself.

So the first thing is my conflict of interest, so the studies I'm going to present today were supported by Cerus and Terumo. I'm poor and I don't get any money from them, just they supported the studies.

Also I wanted to tell you about a study that we did with P-Capt. This is Prion Capture Filter and today I'm really surprised. You know, I'm not European. I cannot donate blood in this country, probably they're waiting for me to die. So the situation is that when I go to Spain I donate blood and here in the United States I cannot donate blood. Of course, in Spain maybe everybody have (inaudible) disease, but the United States maybe nobody has (inaudible) disease. I

don't know, maybe one day the FDA will change their mind, I don't know. Five percent of the donors they have in 2002 they cannot donate. The question is, is there something going to be reviewed or revised? Twenty years with not single one case, I don't know. It's a question I leave to the audience. I don't know about that.

So, but we did the studies. I can tell you in Ireland, they use this P-Capt, prion filters, a physical filter to remove prions because all the symposia has been focused very well in nucleic acid pathogens, but there are other pathogens that do not contain nucleic acid, so what do to with them?

Anyway, so just to let you know that once I have some intellectual property (inaudible), not in the technologies that we're going to talk about today. So the criteria is always the same. It has to be efficacious to eliminate a broader spectrum of pathogens and preventing sepsis. It should be accessible, affordable, and safe. Therefore, (inaudible) may

depend on the use for one single process for a whole lot; should cause minimal cellular damage. There is no compromise to transfusion safety, as it says, by in vitro and in vivo assays and clinical outcomes, minimally toxic, maintain functional cell integrity, and (inaudible) and biosafety. Of course, it will be a miracle that we have all these things together, but this is probably what we need to have or close to if we want to have pathogen reduction accepted by everybody.

So I'm going to start with this slide. It's a very old slide. It comes from the (inaudible) in May 2008, criteria that were defined by the FDA at that time and still today are important criteria to define (inaudible) for licensing. It's not the only ones. It's obvious that in pathogen reduction you have to look at many things, but for red cells this has been one of the major let's say hurdles that has to be passed in order to get the United States licensing or at least moving forward. And I understand, you

know, especially to try to see not just in vitro parameters, but also in vivo, and human response of viability of red cells.

So the in vitro typically is that you have what's called a 9995 rule for red cell mass recovery and (inaudible) leukocyte content and (inaudible) hemolysis of less than 1 percent. But in vivo for the 9570 rule, that means that you have a mean 24-hour red cell recovery in vivo of at least 75 percent with a standard deviation in vivo that (inaudible) 9 percent and ensure that most -- more than 70 percent of red cell products have red cell in vivo recovery of at least 75 percent, which is standard statistical criteria that we could discuss.

So this has been, you know, for many years what we have done and we did multiple studies and collaboration with (inaudible) that has been a master for me for many things. Larry Lamont and Jerry Gotshall, people all over, (inaudible), people are indebted because all of them collaborated with me and simply I only

learned from them.

So this angle to talk about, this is something that we published in a paper -- in a review chapter with Jim many years ago. Now eight years ago. The book, The Penultimate Paradigm. I still remember that. It was a great book. You can still buy it in AABB, so you can go and get it. So that book was about pathogen reduction and one of the chapters I was, you know, honored to write one on red cells and especially we were talking about three different pathogen reduction systems. That there was one, this 303, that is the one that is sponsored by Cerus. The riboflavin with UV light or -- that was sponsored by Terumo BCT. And (inaudible) that now is not being manufactured anymore, but it was used for many years by other companies that then went down in 2003.

So I'm now going to tell about the (inaudible) content. This is the one I just talked to you about, but I want to talk a little bit about the S-303 and the Mirasol. Just I'm

going to give you a summary because I think a lot of information has already been provided, but I think it's always important to have in comparison all of them, what they are (inaudible). So the S-303 is a (inaudible) called FRAIL.

Meanwhile the Mirasol technology (inaudible) or UV light. Photoactivation is (inaudible) for S-303. Mirasol has just has photoactivation and the targets are typically nucleic acids. But in general, the of bacterial reduction when done in optimal conditions, and there have been multiple revisions in the protocols by both companies, is around four to six, three to six locks of depletion. That doesn't mean too much as long as you do these experiments (inaudible) spike in experiments. So it's very hard to know exactly what's going to happen in the field unless you do clinical testing in places where there is a significant amount of infectious transmitted diseases and that's not anymore in America, right.

So both of them produce a leukocyte

inactivation and both of them have some effects that they are not clear on (inaudible). So for instance, S-303 now we have data, at that time, when I put this slide, there was nobody with data, but it looks like has not so much effect on (inaudible) and it looks like Mirasol may have some effect in (inaudible). This is not data from us, but from (inaudible) to you to criticize or not those data.

But just to tell you about the INTERCEPT system, the S-303 as I mentioned, is the great S-300. The system is based on a quenching system (inaudible) on permanent crosslinks the DNA.

So I'm going to give you a small history because people tend to forget these things. In 2003/2004, there were two phase 3 clinical trials. One was in cardiac surgery patients where it was supporting transfusion needs of these patients. One was phase 3 clinical trial in thalassemia and sickle cell anemia. In this second trial there were two subjects that developed antibodies. One was a clear antibody, an IgG. The second one it

looks like it was nonspecific IgM. This complete change to the pattern I can tell you in Cincinnati we were about to transfuse one unit of S-303 red cells in a sickle cell anemia patient and just two hours before the transfusion we were asked to halt the study. So we -- at that time it was complicated. It was hard and, you know, I have to tell you that for Cerus', you know, honor, I think they did a fantastic job because most likely most people have decided to throw up the towel. They took back all the systems to the range and they were able to modify completely the protocol and start from scratch. I think that has a lot of merit.

So during our process use S-303 at.2 (inaudible) added together and the former GCH was free acid with around 20 degrees at room temperature. Then they improved the process with increasing the glutathione at 20 (inaudible) putting the GSH first and then the S-303 and using the GSH as a base, not as an acid, and increasing the temperature of the incubation.

So this second generation system is based on inactivation and removal and then wash. So the red cells are washed after the process. So in phase 1 S-303 red cell studies, so we did one. It was randomized control, single- blind crossover study with two centers in this case and 28 subjects enrolling in the study to ensure 24 subjects available. The study of red cells were stored for 35 days because we already knew that these cells probably would not make it for 42 days and the test system was S-303 red cells in (inaudible), meanwhile the control were conventional red cells in (inaudible). We analyzed a 24-hour recovery on 35-day lifespan of these red cells. We use two layer labels, chromium 51 and technician 99, to do -- they do a label and record (inaudible) study. We evaluate the viability of the red cells after the infusion. We did also crossmatch (inaudible) S-303 during the study using conventional (inaudible). So this study was published and the data I will tell you in a second, but data show in general is that the

date -- the recordings were normal and there was no problem related to antibody formation. The system works very well. In fact, the company, this is not data from me, demonstrated that with this system, with this concentration of glutathione and the concentration of S-303 they were able to completely eliminate the majority of the bacteria and viruses at that time (inaudible). Today now they have a much longer list and I can tell you that in general for the vast majority of them, even non-envelope viruses, they have a significant depletion rate.

They did also (inaudible) and S-303 in animals with this new protocol and they -- I'm not going to get into all the details, but (inaudible) demonstrated that in general using an animal model (inaudible) rats or in beagle dogs, they were able to have no safety signal in those animals.

So then is when they came to phase 2 recovery and survival study. And this is a study we did in -- I'm going to tell you more because we published a year ago. This is crossover trial

where we did a screen randomized between a peer 1 and peer 2 between either INTERCEPT and 303 red cells or control with a storage of 35 days followed by (inaudible) and infusion. In this trial, what we did is to randomize 42 subjects. One was with (inaudible) because of (inaudible) donations. So 41 subjects were the safety population. Out of 10, 2 of them were withdrawn, one either to (inaudible) to collect a unit of blood or because of a normal bili count that prevented the second donation to happen. So in total the population to be analyzed, completed, was 39 subjects. Fourteen of them were not available because of technical issues in one of the centers that collaborated in the study. So in the end we have 26 subjects that were considered efficacy population for analysis.

So in these cases what we found is that the hemoglobin content was very similar between the test lights and control. There was a teeny tiny decrease compared to between the red cells in the S-303 because of the additional wash. There

was a small decline in the hemoglobin at 2.4 points compared with practically nothing in the controlled red cells. When we look at the post-transfusion recording at 24 hours, we found no differences between the control and the test and was not statistically significant. We did see differences in the lifespan and in (inaudible). So what we found is around 17 percent decline in (inaudible) and the lifespan. So that means that the lifespan on the control was around 75 days moved to 63 days in the test and from 39.7 days in the control to 33.5 days in the test. So that was (inaudible). Of course, the criteria of (inaudible) 20 percent even with this case, maybe it will pass. It will have enough power to really define. This was not designed for a non-inferiority design, but we're borderline. So it was around 17 percent difference in this study.

So looking at the recovery study just based on 24 hour recording, based on the FDA criteria, the study showed that, yes we had recorded higher 75 percent with standard

irradiation of less than 9 percent with a number of subjects with recording less than 75 percent only one subject, enough to pass the criteria. So with one study 95 percent confidence (inaudible) for proportion of subjects with at least 75 percent recording higher than 70 percent with 83 percent. So it indicated that, yes, we passed the criteria.

So this, of course, alone means that the FDA criteria for evaluation of these red cells will account that (inaudible) or the S-303 treatment is not affecting the 24- hour recovery. They do have some effect, modest, but some effect on (inaudible) in the survival of the red cells in vivo. This is something that could be relevant (inaudible). Why? Because thalassemia patients or sickle cell anemia patients typically are evaluated because they need chronic transfusions and typically the period of time between transfusion to transfusion is around between three and five weeks, four weeks as an average. And, you know, this could mean that maybe some of these

patients may need one or two more episodes of transfusion a year compared with (inaudible) with the complications associated to that, iron deposits and so on.

So this is just to give you the (inaudible), the average on the numbers. As you can see there's a small difference. So in the blue is the test, S-303 in red is the control. And you can see the difference. It's not big, but there is some difference that you can see. Indicating that really there is a (inaudible) story. So, I mean, while in a 24-hour recovery that has been shown from the times of 1950s that probably is a 15-day storage (inaudible). It's affecting more data in the last 10 years especially, indicating that a storage typically is affecting recovery.

In the case of pathogen reduced red cells, maybe the lifespan is the one that has to be more taken into account. So I think it's important to really measure long term lifespan of the red cells for these products.

Regarding (inaudible) we didn't see any significant ones. There were no SAEs. There were no antibodies being detected, no differences in (inaudible). All the subjects experienced adverse events considered related to studies on (inaudible) transfusions. Five of them during the test period and six of subjects were in the control period, so that was no difference between the periods of the test or the control. So we didn't see any significant effects on adverse events in the subjects. Of course, there were again only a small amount of red cells, so they were getting 10 milliliters of red cells with the (inaudible) label.

So in conclusion for this study that we did in this case, we did with the people in (inaudible) and blood center in Wisconsin University, and (inaudible) along with Cerus is that those red cells did meet the FDA (inaudible) criteria for evaluation on in vivo red cell studies. The recoveries of control red cells were similar when they were stored for up to 35 days,

but the difference is (inaudible) were around 17 percent. We're less than 20 percent, but we were. If we consider 20 percent as the (inaudible) for bioequivalence, we'll be fine. But I can tell you, you know, I was concerned that there could be -- if this had been power enough (inaudible) may not have been passed. (inaudible) crossmatches and the pathogen activated red cells produced -- using the S-303 (inaudible) showed adequate transfusion (inaudible) control red cells.

So we identified the lessons from this study is that we identify that, yes, the S-303 is treating the red cells okay. There is a small decrement in the potency of the product that we define as around 17 percent in the lifespan or health life of the red cells and we don't know what's the clinical results of that. We will think that in chronically transfused patients this may play some role.

So I'm going to tell you about this study and, you know, Dr. Richard Benjamin, has presented this study much better than me, but I

wanted to bring you here very briefly because, you know, I read this study like ten times and this is a phase 2 clinical trial of S-303 in a cardiac study. This is completely independent. It was done in Germany. It is a multicenter trial, very well designed because they need to do not only just a (inaudible), but also have safety measurements, and you know this is where people who were really receiving blood cells. There were patients and they were (inaudible) enough red cells to really make a measurement on that.

So they had in total 87 patients randomized and then allocated to test 45, allocated to control 42. So they have around 45 subjects in each branch to be allocated, follow up. So when you look at the subjects, there was no difference in either renal insufficiency, hepatic insufficiency, or the six minute walk time on the subjects. However, the people in this trial is not powered to really define efficacy. So there was no statistical significant difference, but it's because the number of

subjects that were included was very small. So that part is the part that, you know, disappointed me a little bit because I expected to have a significant group for an efficacy perspective in a clinical trial with a well-powered study.

I mentioned before there were no major differences. There was a trend for (inaudible) in the test, but they never reach any statistical significance, although four assays (inaudible) borderline and there you can see a small trend to have (inaudible), but they're trends. Nobody knows. The study has no power, it's very hard to make an accomplishment out of that. So no treatment differences observed in the usage of red cells to support acute anemia or in clinical outcomes (inaudible) such as renal or hepatic failure, although the study as I mentioned was not powered to differentiate (inaudible) clinical endpoints.

So I understand this was mostly as priority phase 2 and it has to be followed up by a good phase 2 or a phase 3. So I was very happy to

hear Dr. Benjamin who was presenting the phase 3 clinical trial done in Turkey and Italy, and I'm really here to see the paper published. I think it's very important for the field to have real data on patients using S- 303 red cells.

(inaudible) more corrected to surgical complications, not really differences with the randomization. The group, the study group, the clinicians who did the study, this is very interesting because they discouraged the use of the six-minute walk test to (inaudible) measurement of red cell function, oxygenation in this use. They said it is very hard. In fact, I didn't mention very much, but the standard irradiations that they reported were humungous. So (inaudible) are more than 100 percent. It is very hard to really make interpretations and in

designing this study that could be powered enough to really define differences with this kind of standard irradiations.

So the other studies I'm going to tell you is about, you know, we work with everybody. We try to test technologies and we try to test them in an independent as possible manner. So the other one is about riboflavin and UV light. So this is the invention by Terumo BCT and in this case is riboflavin in saline plus UV light. The process is only taking one hour and there's no wash, so that's good. There are two types of reactions, one is oxygen dependent and one is oxygen dependent that changes reactive oxygen species.

So one of the two things that I have to say is that in general these two technologies have something in common. It's that they use a chemical more (inaudible) in the case of riboflavin and (inaudible) in the case of S-303 that really bind to nucleic acids, no question,

but they bind to many things and they produce many other things. One of them is reactive oxygen species. So it is possible that they will identify a way to notify the chemistry of this compound or modify the reactive oxygen species production. We may see a significant reduced impact of this technologies into the viability of the red cells or other (inaudible) or so on. So I think that there's a window of opportunity here and we understand very well how to target this.

So the whole blood PR Mirasol technology is based on (inaudible), very simple. This is (inaudible) and you put it in the machine and typically in around one hour you are ready to go. So the Mirasol system has all these things so it has been CE marked, but there's no licensing in the United States, and red blood cell in vivo therapy remains (inaudible). First there's the advantage of simplicity, course of action, and use of implementation.

We did some studies ourselves and other studies done by Terumo with human whole blood and

they found that the leukocytes were equally inactivated. The (inaudible) production was decreased with doses as low as 22 to 44 (inaudible) per milliliter of red cells. And they were able to identify significant PRs with 1.8 to 4.6 logs when they used 80 (inaudible) per mil of red cells. So, of course, 80 (inaudible) per mil of red cells is a lot of energy. I can tell you that you can feel it that the red cell unit is warm, more than warm, it's literally hot when you leave from the illuminator. So that's something that I don't think it's good, but I can tell you that this has a payoff. The payoff is that the lifespan or the ability to store the red cells for a long time is significantly reduced.

I'm going to share some data how we find out about that. So the illumination (inaudible) correlates with our red cell recovery and we published that many years ago. Also, we knew that the 42-day stored red cells produced from the whole blood treatment deteriorated earlier during (inaudible) units. So based on that and the data

from Susan Marchner and that inability to deplete pathogens, we decided -- and also data from Terumo as well that they (inaudible) years ago, but they demonstrated that in a model. And this is very nice because they use a humanized animal model, so a (inaudible) mouse, where (inaudible) demonstrated that the graft (inaudible) produced by T cells in the graft was significantly declined when they use either gamma irradiation or they use the Mirasol technology for illumination of the red cell and they compare. (inaudible) polysaccharide or (inaudible) and they were able to see that all the inflammatory seen (inaudible) to the infusion of red cells they're having treated with Mirasol or (inaudible). When they did it (inaudible) model in the control all the mice tend to die. As you can see, this is (inaudible) while the mice that received either irradiated products or Mirasol ones survive. And when they look in the model (inaudible) the inflammatory signaling was significantly abolished for both gamma irradiated and for Mirasol treated ones.

So this was very interesting and this has been reproduced with the Cerus INTERCEPT system. So although (inaudible) recently, very recently, a month ago, I think, is the paper out, that they saw more or less the same affect in a different assays, not in vivo, in vitro, in culture systems, but they found also that their technology was able to prevent the presence of alloreactive T cells.

So as I mentioned before this is the component, so this is (inaudible). First of all, we did some in vitro experiments. This is whole blood and this is the big difference with the studies we did with the S-303. S-303 we used red cells, the conventional red cells in AS-5.

In the case of whole blood, what we did is -- we did, first of all, some experiments. And these experiment is what we did is to store the red cells for longer times and we did day 21, 28, 35, and 42. And you can see here the ATPs start declining after around day 28, but especially what you see is that the hemolysis start increasing and

the potassium is significantly high. So based on the data of hemolysis, and you can see day 28 had the high hemolysis with a huge standard deviation indicating that we are borderline, we decided to do studies on day 21.

So the storage of the red cells coming from whole blood irradiated with Mirasol and riboflavin, this study I'm going to show you, were the storage of only 21 days. You know, I'm the guy (inaudible) blood center. If I have to have all my blood units after 21 days that would be a big problem for me. I'll be blunt, but I would understand that the military or in other circumstances that probably this is appealing to them, to have 21-day red cells or in the cases, for instance, recurring transfusion, thalassemia patients in Italy for instance, where the majority of the patients are getting red cell units of less than 10 days, this is probably a very different situation. In the United States, we still depend of longer storage of red cells.

So we did this study as well, an

analysis of the chromium 51 illusion rate. So this is important when you do these studies. We did also for the S-303, I didn't mention to you, but you want to be sure that the technology is not really affecting your readout. In this case, is the chromium 51 release and we did a very nice study on that. This is with (inaudible) we did a very nice study. And we show no difference between the control on the Mirasol S-303 red cells in relation to chromium illusion in an in vitro surrogate model.

So the aim of this study wasn't to therefore evaluate the in vivo performance and record the survival of 21 days stored red cells, they are for whole blood treated by the Mirasol pathogen reduction system for whole blood as I mentioned. And the primary endpoint was red cell recovery at 24 hours and this (inaudible) red cell survival, half-life, and (inaudible) and (inaudible) correlations.

And also we wanted to know (inaudible) whole blood (inaudible) for stored red cells and

the safety of this was. One point I mentioned not enough, but I wanted to bring up, you know, one of the key points when we irradiate, gamma irradiated or Mirasol or S-303, you know, we put UV light and this is typically the light source. We see these increases in potassium. So, you know, one of the things I always wondered myself is what's the mechanism of the potassium leakage of the red cells when there is post- irradiation? You know, I read all the literature. The literature is very old. It comes from the 1950s on why red cells leak out potassium and there were all these theories, also sodium potassium ATPAs and loss of function of that. You know, (inaudible) clearly demonstrated that that's not true. It's not our sodium potassium ATPAs.

So people now believe that the (inaudible) specific leakage. I kind of believe that. I think it's hard for me to believe that the way how gamma irradiation or UV light works is just, you know, some kind of leak syndrome of the cell. You know, that I lost the potassium. I

think that probably there's a lot to understand. We know more about (inaudible) than we knew a few years ago. We know, for instance, in sickle cell anemia how important our dose of potassium (inaudible) that we have not done a good job in trying to understand the mechanism how potassium leaks out of the red cells. One problem that is still very clinically relevant especially in pediatrics.

You know, it's not nice when a cardiac surgeon calls you, telling you that by mistake your technicians have sent a red cell unit to the cardiac operating room that was close to the expiration time and the potassium in the subject after changing the cardiac (inaudible) solution, which is 7 milliequivalents per liter, he couldn't restart the heart. That was not nice and sincerely I understand the surgeon that he was sweating. So for me this is very important.

So this study is our perspective to (inaudible) single-blind, randomized (inaudible) crossover study (inaudible) 21 days storage and

randomize leukocyte reduced red cells. And we infuse (inaudible) red cells and we look at that within the two arms. They are very similar to the nine subjects enrolled, 24 were (inaudible). Five of these 29 subjects discontinued prior to day 21. And (inaudible). I can tell you some of them is because I felt that they were not going to be compliant with the process of coming every few days to collect a specimen for analysis and one of them because we threw the consent. So this was the data.

So this is two sites and this is in collaboration with (inaudible) in Bloodworks Northwest. We did very good work together so we used the same protocol. I flew to Seattle and we put together the same protocol between (inaudible) and myself, and it worked very well. The study was very well defined. So we measured the hemolysis and you can see there was no difference between site one or site two between the untreated and Mirasol and there was no difference in the chromium 24-hour recovery (inaudible) red cells

between the site one and two, untreated or with Mirasol treatment. So that was telling us that, you know, two laboratories that used the same protocol, but they were independently in doing this, found similar or the same results.

So the primary endpoint taking together the full cohort of 24 subjects between the two centers is that the Mirasol and red cells have a survival -- 24-hour recoveries of 83 percent, (inaudible) 92 percent. So despite they were stored only for 21 days there was a 8 point difference between the untreated and the Mirasol. It fulfilled the FDA criteria, but for me at least I can tell you that there was a significant decline in the potency of the product. This, by the way, was on day 21. The (inaudible) within what was expected and it passed the criteria for the FDA for day 21, evaluation criteria.

The survival similar to the S-303, we show a significant decline. The decline was significantly more. We saw around 21 points, around 30 percent decline in the survival in the

remaining days. Also similar in the (inaudible) of the red cell survival was also highly declined, around 15 percent. We saw that for the first time, and I can tell you I do these studies all the time, most of the times I never see a correlation between ATP levels and recovery of the red cells or survival, but I do see when we use UV light. When we use UV light the ATP levels correlate perfectly with the red cell recovery and survival very well.

So we look at the metabolic status and the hemolysis. As I mentioned there was more hemolysis in the Mirasol group. It still was within the regulatory levels, but higher. The ATP was lower, (inaudible) lower, but was lower, around 10 percent lower from 5 to 4.4 (inaudible) per gram of hemoglobin and the sodium potassium was high, around 66 milligrams per liter, but that was very comparable to the gamma irradiated red cells. Meanwhile the (inaudible) control had 37 milligrams per liter of potassium at that time.

There were no significant adverse events

and no difference between the two groups. Again these people receive only 10 milliliters of (inaudible) label red cells. We didn't expect any problem in such a small transfusion.

So in conclusion for this study is that the 21-day stored red cells, they are from Mirasol treated whole blood (inaudible) according to FDA criteria. However, we see a significant decline in the potency of the product regarding viability at 24 hours and survival. No safety issues (inaudible) in this dose. We looked at antibodies as well and we didn't see that.

So, however, the results of these red cells look very similar to the published data for gamma irradiated red cells. And in gamma irradiated red cells we have, you know, 28 days for storage. So, you know, looking at everything to be fair, we see just compared with our control with non- irradiated they are significantly inferior, but not much more inferior than gamma irradiated red cells that we use routinely for patients immunosufficient. (inaudible) for single

cell.

So I'm going to give you some final reflections based on my modest experience and experience of the group on pathogen reduction of red cells whole blood. I think there has been a huge advance if I compare with 15 years ago and no question, we have learned a lot in these last 10 to 15 years about how to modify and tweak protocols. I still believe that we are still not there. We are not at a sweet spot, not even close. I think we have to do better and we can do two things. One side is to ameliorate the issues that we have recognized. Second is that we can't really identify mechanisms why these issues come up and then try to see whether we can target them.

And finally, we have to find a compromise.

(inaudible) that if we believe, and I do believe, that transmission of infectious diseases in chronically transfused patients is a problem and this is a problem that every

thalassemia or sickle cell anemia doctor will tell you that there is concern about, has to merge with a situation where we are not going to significantly or (inaudible) increase the number of transfusions into the patient simply because the red cell half-life or survival has declined. So (inaudible) I think can be achievable. It can be achieved.

I think that we need to (inaudible) about the cost of this implementation, so what I like a whole blood pathogen reduction is that inferior at least, this should be the way to really reduce the cost, make these technologies feasible and available to many health systems that otherwise they could not afford it. The question is how technically to achieve that and I think still we have to learn a lot.

I know, Dr. Benjamin and Dr. Razatos have presented some very interesting developments

about clinical trials, phase 3 clinical trials in using these technologies (inaudible). They did a fantastic job in presenting them. (inaudible) that this is the way to go to see in phase 3 clinical trials how they behave.

I think, personally I'm hopeful. I don't know if it will take us another 50 years to have red cells license, but I think we'll be able to do it. So 10 years ago, sincerely everybody thought we were not going to have platelets, pathogen reuse in the United States and we do have it. So maybe there is room for optimism (inaudible) and pathogen reduction in red cells in whole blood.

I am going to leave it there. These are the people who did all the work. I don't do anything. So Anita, especially all the group, Anita, (inaudible). The group by Larry Lamont. He's now in Denver, but at that time he was in Dartmouth Medical School, along with a group in (inaudible) led by Jerry Gotshall did fantastic work. And, of course, (inaudible) at Bloodworks

Northwest and all her group in (inaudible) with both one side Cerus and the other side Terumo, led by Larry Corash and Ray Goodrich. Thank you, everybody, and thanks for your attention.

(Applause)

DR. GOODRICH: Okay, we ran a little bit over because my phone died and I was afraid to stand up. But we do want to take some questions from the audience or from people on the phone if we can. Are there any questions for any of the panel members?

MR. GONZALES: This is Rich Gonzales or Rich from Biologics Consulting. I've been involved in PRT for many, many years and actually when I was in uniform I approached both companies to see what they could do for whole blood because of the military need. But the question I have is for Dr. Benjamin.

On the German study and the Turkish study that were done, that were published, I notice that there were -- they didn't include all the blood types, for example, the German study

only included the A and O patients. Is there any plan to look at all the blood types to make sure that there's no issues with all those patient populations?

DR. BENAJAMIN: Let me correct you. The study in Izmir and Turkey was with all the blood types. You haven't seen it because it isn't published yet, but it was. So the German study was a phase 2 study and given the difficulty in identifying those patients and the nature of the study it was restricted. That's not the case of any of our other studies.

MR. GONZALES: So all of the studies there will be -- include all blood types?

DR. BENJAMIN: All the studies ongoing including one of our U.S. studies that are ongoing. We have enrolled already more patients in the U.S. than were involved in the European studies and it involves all blood types.

MR. GONZALES: Okay. Thank you.

DR. AUBUCHON: AuBuchon, Seattle. Jose, this question comes from your very thorough

presentation, but it probably needs to be answered by other members of the panel. You showed data that the INTERCEPT system for red cells yields acceptable recovery after 35 days of storage and Marisol red cells at 21 days of storage. I don't think that any of the laboratories that do this kind of work have ever been asked to or have ever taken on pushing the envelope to see how far out we could store these red cells because with recoveries in the mid 80s at one seven-day breakpoint, you would think you could probably go another seven days and still meet the FDA recovery criteria.

So what does that mean? Well, a 35 day red cell, I could probably handle that inventory wise, 21 days that would be quite a challenge, 28 would be better, that might have chance at succeeding and, certainly, 42 would be better than 35. Now, do we really need that extended storage? I ask the question because it is important. I mean, all blood collectors in the country are challenged, not only by total collections, but by

the increasing amount or increasing proportion of group O red cells that are required of us. And the group O red cells are a problem because they do get consumed in trauma and everyone wants to be a level one trauma center it seems, but also the smaller hospitals that have group O on their shelves are reluctant to transfuse that to anyone else until it gets close to outdated. And then they don't want to outdate the group O, so they give it an A or a B, and that really is a waste of that group O donation.

So as the storage period for red cells is shortened by these techniques, possibly shortened, we will be additionally challenged to keep enough O on the shelves. It will make the O "overutilization" problem even worse. So I don't know if representatives from the two manufacturers would like to talk about the potential for extending these studies to 42 days for INTERCEPT and 28 days for Mirasol.

DR. RAZATAS: So right now for Terumo BCT, in studying or in developing study designs we

pick our most likely chance to win, right? And so when we're getting to radio label recovery and survival studies or we're getting into clinical studies we're picking the time point that we have the highest confidence of passing the FDA criteria. So it's really, you know, completing the PRAISE clinical study, you know, getting FDA approval and then as we move forward with, I showed you, you know, kind of our next generation device and vision, you know, at that point that would be an opportunity to push the envelope further, so.

DR. BENJAMIN: I think my colleague makes a good point. You pick a number to win. Having said that, we are very happy with the recovery and survival we have. There are other parameters that you have to consider too such as hemolysis and I did show data to show that actually our hemolysis 35 days was superior. It looked better than control. I don't know about superior, statistically. There is ATP levels -- ATP levels are higher than the controls at 30 --

day 35 and so all the parameters we've looked at actually might suggest that we could push further if we chose to spend another half million dollars on -- you know, because you have to choose this upfront, so another half million we could have a look at it.

QUESTIONER: I have one comment and one question. Dr. Goodrich made a prediction for (inaudible) 18 to 20 years. He can check one of them because energy and technologies are here. We are supposed to start a company in Worcester, Mass., and hopefully some of you learn about our innovative technologies. This is most of challenges you just mentioned.

And now a specific question for Dr. Cancelas, if I'm pronouncing it appropriately. You mentioned you are, I think, pathogen inactivator such as S-303 and (inaudible), simultaneously. And the question is, you know, logically it would be first to inactivate and then residual amount to quench. It sounds like you are pushing at same times brakes and gas. That's one

question.

And second question would be also you mentioned you are washing, if I understood correctly, the process includes washing after inactivation and what would be the main reason why you need to wash? Thank you.

DR. CANCELAS: So thanks. The first question, well, the reason was because the protocol changed. In order to have the buffer capacity before, in order to be absolutely sure that there was all this because there is not my invention, so this was something designed by Cerus Corporation. And they found and they have data that clearly show in vitro that by doing that they had less degradation of the (inaudible 46:51.2) moieties in the red cells. And that was also the use in vivo animal model, a rabbit, a (inaudible) animal model, where really they demonstrated that that approach by changing the timing where they put the glutathione (inaudible) S-303 significantly declined or reduced the amount of (inaudible) moiety binding to the red cells. And

that was the belief and I still believe that is the major source of what at that time people developed antibodies. So the (inaudible) of new antigens that could be developed on the red cell surface. That's the reason why they made that change.

The second part was -- I'm sorry, what was the second question?

QUESTIONER: You mentioned that you also apply washing after (inaudible).

DR. CANCELAS: Yeah. So the washing is the same situation. So the idea was so to reduce as much as possible any remaining amounts of either S-303 or the byproduct S-300, although the byproduct is not alkaline and is not binding in itself, but there was belief that there was good from that same point of view to remove it. The FDA wanted that as well. So the FDA said the only way we can think that you can go forward and maybe, Richard, you can tell me more about that, but my understanding from what I was told, I was not in those conversations, is that the FDA and

Cerus agreed that was a step to help to move forward the protocol after the development of the two situations of (inaudible) in the first protocol being implemented. This was in around 2006/2007.

QUESTIONER: Thank you very much.

DR. BENJAMIN: Maybe I can just add to that before you step back. Indeed, we wanted to reduce the byproducts, but there was a second reason and that was it gave us an opportunity to add a new aliquot of additive solution, a fresh aliquot which actually boosts the ATP levels of the red cells and makes them more healthy. Because we have had that 18 to 24 hours of room temperature hold during which time the red cells are metabolizing and so there's extra metabolism that we have to deal with. Our red cells look more like the European, you know, room temperature overnight red cells than the U.S. Of, you know, put into 4 degrees upfront. So we were able to add a new fresh additive solution and boost the ATP levels et cetera, in the red cells by doing

that wash.

QUESTIONER: This creates next question then, it is one single wash you use or several washing have been added, too?

DR. BENJAMIN: It's a single supernatant replacement. "Wash" is a strong word. However, having said that, our products actually -- because we now further reduce the protein levels in the supernatant, we fully meet the European requirements to be a washed red cell. We have on average less than, I think, 70 or 80 milligrams of protein plasma protein left, which robustly meets the washed red cell requirement and it will be interesting in clinical studies to look at things like allergic reactions and trolley in the long run, although we haven't powered our studies to look at that at this point.

QUESTIONER: Thank you very much.

QUESTIONER 2: I thought all the talks were great, so thank you so much. I had a question about the high potassium levels in both technology. That might make it very difficult to

have this product for the NICU population or massively transfused population or even, you know, large volume transfusions in the OR. What are some mitigations you have to start thinking about to deal with the high potassium?

DR. RAZATAS: So those are some of the reasons that for the study we're limiting to 21 days and that's kind of the payoff is you can have longer storage with more degradation in red blood cell quality or go back.

QUESTIONER 2: I thought the potassium levels were going up sooner than that? Like on day 7?

DR. RAZATOS: In the dataset that I presented from Trackman it's about the same. It was the same between test and control up to 21 days and then it just depends on which data study you're looking at and then also on the red blood cell storage solutions. So, but you were talking about Jose's data.

DR. CANCELAS: What we saw is that -- we saw a really significant increase in the

potassium. So, of course, the control increases and the test increases, but we saw that the test also had highly more potassium data control. It was not a huge difference in day 7 and day 14, day 21 was more, and then you go even further the difference splits much higher. So the potassium leakage exists.

Now, that's a good question, how to remove that. So people are working on trying to identify, make any sense of filtering out potassium and there are people who have very good cartoon observant columns that now are being developed. I think that that's probably the way to go. We want to go for pathogen (inaudible) will have to be integrated. This is my personal view. I have nothing to do with the companies.

DR. BENJAMIN: Maybe I can just address that. The potassium levels if you compare ours to irradiated red cells, we're actually superior, were actually better.

QUESTIONER 2: Well a lot of people have moved to just-in-time irradiation just for that,

you know.

DR. BENJAMIN: In comparison, if I recall the data, in comparison to conventional red cells were not worse.

DR. RAZATA: And I think there's just the potential to address it would be looking at different red blood cell storage solutions. So that's one avenue if that becomes a major concern of addressing that.

DR. CANCELAS: So the potassium problem was mostly when you irradiate. So it's the UV light and it is the irradiation. The S-303 potassium is not significantly increased. In fact, with the washing they see even, you know, we saw less potassium. Where we see the potassium is when you gamma irradiate and this (inaudible) irradiation or when you use UV light. That is when you see the potassium leakage.

So is there energy? Is there heat is what really, you know -- not the heat, because gamma irradiation, that's (inaudible), but it's just the ionizing irradiation what really is

making a difference there, my point of view. In the S-303 I don't see that as a problem. I think there are other issues with S-303 (inaudible) binds to proteins, (inaudible), and all these things, but that's a completely different story.

QUESTIONER 2: I have another quick question. Well it may not be too quick. I'm really intrigued with the idea of, you know, treating the whole blood and then manufacturing components from -- that are all pathogen reduced. Most of the talks were focused around the red cells and functionality of the red cells. Could you share what you know about the functionality of platelets in plasma for that technology?

DR. RAZATOS: So, Dr. Trackman, data that I presented was on red blood cells and so the next phase of his study is going to be looking at transfusion of plasma for Mirasol treated whole blood and then we are doing internal studies looking at platelet quality and it just -- it depends on if it's random donor platelets, buffy coat platelets, Reveos platelets, whole blood

automation, and so those are all things that we're exploring. We're seeing good platelet quality coming out of that, it's just fine-tuning the process and then picking the right process to combine technologies.

DR. GOODMAN: I think there's some published data that Dana Devine did with whole blood separating the components. We'll take two more questions from Steve and Dana and then if there are any on the phone, I think, and then we should probably --

DR. DEVINE: I just want to comment on that. What we've shown (inaudible) is that if you look at Mirasol treated platelet concentrates and compare them to the platelets that you derive from whole blood that's been treated in the Mirasol process, the platelet quality parameters are better in the whole blood treatment than to treat the platelets themselves. Presumably there's some protection of the damage by all the hemoglobin that's present in the whole blood.

SPEAKER: Just to add to that, so Dana

did that study with buffy coat method. We've done it with the PRP method and actually the second hard-spin really affects platelet quality. It tends to clump them. So it depends how you make the platelets.

QUESTIONER 3: Just with this discussion of red cell quality and Richard's comment that we could do something different if we spent a lot more money to re-go back. I'm wondering if we're going to be in the same situation with red cells as we are in platelets. The regulatory agency says you can -- if you can collect on one device and one solution it's valid, but if you want to collect in a different red cell solution start from the beginning again and invest another $10 million. Do you think that -- which obviously is not very practical until you actually sell some product, so do you think that you basically make your choice now which solution you're going to use and there's no flexibility?

DR. BENJAMIN: It does matter which -- so we start off with a packed red cell. So we get

to choose what solution we put that packed red cell into before we start off with pathogen reduction and then we get to choose what additive solution we add at the end. Because we start off with packed red cells we can collect in the bag and the right bag for our process. Having said that, our process currently is optimized for SAGM, which is not a U.S. system, which means that we are in the process of validating the system for AS-1 and AS-3 at this point.

So, yes, we are doing the work upfront and we expect to come, you know, to a PMA in the U.S. in appropriate additive solutions for the U.S. Our final additive solution after our wash is still probably going to be SAGM because that's part of our system.

DR. GOODRICH: Okay I want to thank the speakers again for excellent presentations, myself excluded, of course. Thank you. And if, Dr. Atreya would like to say any final words or invite the group back for tomorrow? There is a shuttle that's available at 5:30 for those who are staying

at the Courtyard Marriott in downtown Silver Spring that will arrive here.

Thank you all. Please come back tomorrow. I think it will be some additional very interesting presentations.

(Whereupon, at 4:30 p.m., the MEETING was adjourned.) * * * * *

(Whereupon, at 12:34 p.m., the PROCEEDINGS were continued.)

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CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

I, Carleton J. Anderson, III, notary public in and for the District of Columbia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public, in and for the District of Columbia

My Commission Expires: March 31, 2021