The above-entitled matter met in Salons A, B, and C of the Hilton Washington, D.C. North, 620 Perry Parkway, Gaithersburg, Maryland, at 8:00 a.m., Charles E. Edmiston, Jr., Ph.D., Chairperson, presiding.

PRESENT:
CHARLES E. EDMISTON, JR., Ph.D, Chairperson
MATTHEW J. ARDUINO, D.Phil, Voting Member
RICHARD O. BUTCHER, M.D., Voting Member
YARDIN B. DAVID, Ed.D., Voting Member
BONNIE M. WORD, M.D., Voting Member
TERRY LAYTON, Ph.D., Industry Representative
CAROLYN N. PETERSEN, M.S., Consumer Representative
CHIU S. LIN, Ph.D., Director, Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices
SCOTT A. COLBURN, BSN, RN, LT, USPHS Executive Secretary

FDA PRESENTERS:

THOMAS GROSS, M.D., M.P.H., Director, Division of Postmarket Surveillance, Office of Surveillance and Biometrics
SHEILA MURPHEY, M.D., Chief, Infection Control Devices Branch
ANTHONY D. WATSON, M.S., M.B.A., Chief, General Hospital Devices Branch
JASON F. LIPMAN, Lead Reviewer, General Hospital Devices Branch
SHEWIT BEZABEH, M.D., M.P.H., Medical Officer, Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices
DAYAWANSA G. RANAMUKHA-ARACHCHI, Ph.D., Molecular Biologist/Genomics, Office of Science
and Laboratories, Division of Biology

**INVITED GUEST PRESENTER:**

MARTIN FRIEDE, Ph.D., Initiative for Vaccine Research, World Health Organization

**INDUSTRY PRESENTERS:**

DARIN LEE ZEHRUNG, Program for Appropriate Technology in Health (PATH)

MARK KANE, Program for Appropriate Technology in Health (PATH)

LINDA D'ANTONIO, D'Antonio Consultants International

KATHLEEN CALLENDER, Genesis Medical Technologies

**PUBLIC SPEAKER:**

HARRY HOOKS
HCVets.com

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Dr. Murphey, Chief Infection Control Devices Branch

Mr. Watson, Chief, General Hospital Devices Branch

PUBLIC HEARING SESSION

Harry Hooks, HCVets.com

PRESENTATIONS BY FDA

Introduction and welcome,
Mr. Watson

Mr. Lipman

Dr. Bezabeh

Dr. Ranamukha-arachchi

Questions by Members to FDA presenters

PRESENTATIONS BY CDC AND WHO

Dr. Friede, WHO

PRESENTATIONS BY INDUSTRY

Dr. Zehrung, PATH
CHAIRMAN EDMISTON: Good morning. I'd like to welcome to the 35th meeting of the General Hospital and Personal Use Device Panel. I also want to request everyone in attendance at this meeting to sign in on the attendance sheet that is available on the table outside the door.

I will note for the record the voting members present constitute a quorum as defined by 21 CRF Part 14.

At this time I would like each panel member at the table to introduce him or herself and state his or her specialty position, title, institution and status on the Panel. And I'll start with my left, Dr. Lin.

DR. LIN: Hi. Good morning. My name is Chiu Lin. I'm the Director of Division of
Anesthesiology, General Hospital, Infection Control and Dental Device in FDA.

MS. PETERSEN: My name is Carolyn Petersen. I'm a web editor at Mayo Clinic in Rochester, Minnesota. And I'm here as the consumer representative.

MR. DAVID: Good morning. My name is Yardin David. I'm Director of Biomedical Engineering Department at Texas Children's Hospital in Houston and Assistant Professor at Baylor College of Medicine, Department of Pediatrics.

EXECUTIVE SECRETARY COLBURN: Good morning. My name is Lieutenant Scott Colburn. I am the Executive Secretary to the General Hospital and Personal Use Devices Panel.

CHAIRMAN EDMISTON: My name is Charles Edmiston. I am a faculty member at the Medical College of Wisconsin and hospital epidemiologist.

DR. WORD: Hi. My name is Bonnie Word. I am on faculty at Baylor College of Medicine also at Texas Children's Medical Center where I'm the Chief of the infectious disease clinic and travel medicine clinics.

DR. ARDUINO: Hi. My name is Matt Arduino, and I'm the lead microbiologist in the epidemiology and laboratory branch at the Division of Health Care Quality and Promotion at the Center for Disease Control and Prevention.

DR. BUTCHER: I'm Richard Butcher, a physician at San Diego, general practice with Care View Medical Group.
DR. LAYTON: Good morning. I'm Terry Layton, a biomedical engineer. I'm industry representative on this Panel. And I'm from Laytech, Incorporated out of Chicago, Illinois.

CHAIRMAN EDMISTON: Thank you.

Lieutenant Scott Colburn, the Executive Secretary, would like to make some introductory remarks.

Lt. Colburn?

EXECUTIVE SECRETARY COLBURN: Before I start the remarks, I'd like to introduce Ms. Mary Ann Killian from the Ethics Integrity staff to read the conflict of interest statement for the members of the Panel.

MS. KILLIAN: Thank you.

The Food and Drug Administration is convening today's meeting of the General Hospital And Personal Use Devices Panel of the Medical Device Advisory Committee under the authority of the Federal Advisory Act of 1972. The Advisory Panel meeting provides transparency into the Agency's deliberative processes. With the exception of the industry representative, all members of the Panel are special government employees or regular federal employees from other agencies and are subject to the Federal Conflict of Interest laws and regulations. Consequently, in the interest of transparency and the spirit of disclosure, the following information on the status of this Advisory Committee Panel's compliance with the Federal Ethics and Conflict of Interest laws covered by but not limited to those found at 18 USC 208 and 21 USC 355(N)(4) is being provided to the
participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal Ethics and Conflict of Interest laws. Under 18 USC 208 Congress has authorized FDA to grant waivers to special government employees who have limited financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Members and consultants who are special government employees at today's meeting have been screened for potential financial conflicts of interest of their own as well as those imputed to them including those of their employers, spouse or minor child related to the discussion of today's meeting. These interests may include investments, consulting expert witness testimony, contracts grants, creative teaching, speaking, writing, patents, royalties and primary employment.

Today's agenda involves a discussion on methods to assess the potential of disease transmission by multi-use nozzle jet injectors; that is jet injectors for which the fluid path for the injection is used more than once. The discussion will also include premarket testing, recommendations to address this issue. This is a general matters meeting during which the topic of discussion is limited to recommendations or considerations of broad legislative proposals, regulatory initiatives or policy developments that affect an industry, group of manufacturers
or health care providers. So any conflict of interest waivers granted for this meeting are broad and general in nature.

A copy of the written conflict of interest waiver statement may be obtained by writing to the Agency's Freedom of Information Office, 12A30 of the Parklawn Building.

Based on the agenda for today's meeting and all financial interests by the Panel participants it has been determined that all interests in firms regulated by the Center for Devices and Radiological Health present no actual or appearance of conflict of interest for today's meeting.

The following Panel participants have not received a conflict of interest waiver to participate in today's meeting: Dr. Charles Edmiston, Dr. Matthew Arduino, Dr. Richard Butcher, Dr. Bonnie Word, Dr. Yardin David and Ms. Carolyn Petersen.

In addition, Dr. Terry Layton has been invited to participate as the industry rep acting on behalf of all related industry, and is employed by Laytech, Incorporated.

With regard to FDA's guest speakers, the Agency has determined that the information provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers:

Dr. Bruce Weniger, who is a guest speaker with us today, has acknowledged that his employer, the Centers for Disease Control and
Prevention, has financial interest in firms at issue. The financial interests and professional relationships are in the form of research contracts and educational projects involving multiple-use jet injectors.

Dr. Martin Friede, who is also a guest speaker with us today, has acknowledged that his employed the World Health Organization has interest in today's topic in the form of pending clinical trials. As guest speakers, these individuals will not participate in Panel deliberation.

Members and consultants of the Committee are reminded that if the work of the Committee moves from matters of general applicability to matters that are more specific, for example product or firms identified, the FDA shall end the discussion promptly and each special government employee's financial interest will be reexamined in relation to the particular matters so that a determination may be made on whether exclusion from further discussion is required. All exclusions will be noted for the record.

Finally, in the interests of public transparency with respect to all other participants, we ask that they publicly disclose prior to making any remarks any current or previous financial involvement with any firm whose products they may wish to comment upon. This statement will be available for review at the registration table during this meeting and will be included as part of the official meeting transcript.
Thank you.

EXECUTIVE SECRETARY COLBURN: Thank you, Ms. Killian.

The FDA seeks communication with industry and the clinical community in a number of different ways. First, FDA welcomes and encourages premeetings with sponsors prior to all IDE and PMA submissions. This affords the sponsor an opportunity to discuss issues that could impact the review process.

Second, the FDA communicates through the use of guidance documents. Toward this end, FDA develops two types of guidance documents for manufacturers to follow in submitting a premarket application. One type is simply a summary of the information that has historically been requested on devices that are well understood in order to determine substantial equivalence. The second type of guidance document is one that develops as we learn about new technology.

The FDA welcomes and encourages the Panel and industry to provide comments concerning our guidance documents.

I’d also like to remind you that the tentative dates for the next meeting on the General Hospital and Personal Use Devices Panel is scheduled for September 27, 2005. You may wish to pencil in this date on your calendar, but please recognize that this date is tentative at this time.

The first item on our agenda is a presentation by Dr. Tom Gross from the Office of Surveillance and Biometrics. He will discuss the
conditions of approval studies and recent changes in CDRH.

Dr. Gross?

DR. GROSS: Good morning.

As was stated, I'm Tom Gross. I'm the Director of the Division of Postmarket Surveillance in our Office of Surveillance and Biometrics. And I'd like to take a few minutes of your time today to talk about recent changes in our conditions of approval study program.

Before I do that, I'd like to touch based on some of the essential functions that our office serves for the center. And those are presented in this slide here.

First and foremost, we provide support for premarket review. We have a large group of statisticians who address all statistical aspects of premarket submissions. We also have a group of epidemiologists who are involved in PMA review teams and help design condition of approval studies.

We are also responsible through our nationwide passive surveillance systems to detect signals of potential public health problems. That's our Medical Device Reporting system or MDR system. And our network of user facilities throughout the United States for our MedSun network.

Thirdly, we're responsible for risk characterization and analysis of these potential public safety issues. This is done primarily by our epidemiology staff doing everything from systematic literature reviews to de novo studies.
We also coordinate our center response on these public health issues. We convene committees of center experts to deliberate these issues and to present their recommendations to center senior staff for action.

And lastly, we have a staff who interpret our medical device reporting regulations; what needs to be reported under what circumstances, and also to follow-up on violations of those reporting requirements.

Now let's turn to our condition of approval study program. As most of you know, these studies are ordered as a condition of approval of our PMA products. And the regulations clearly stipulate the following:

That post approval requirements can include continuing evaluation and periodic reporting on the safety, effectiveness and reliability of the device for its intended use. This regulation gives us our broad authority in ordering these post approval studies.

Next slide.

Now about the middle of 2002 our office took a snapshot of the center's activities with regard to the condition approval study program to see how well the center was doing. And the study basically involved looking at PMAs that were approved from 1998 through the year 2000. All tolled, there were 127 PMAs that were approved during that period of time. 45 of those had clinical condition of approval study orders.
At the end of the day what did we find? That CDRH had limited procedures for tracking study progress for results, that our IT and other systems were wholly deficient in this regard.

There's large turnover of lead reviewers that resulted in lack of follow-up. Up to 40 percent of individuals who are lead reviewers at the time the PMA came in the door were no longer associated with that PMA when we did this study.

And lastly, there was lack of premarket resources. Those resources were devoted to premarket submissions and there was little left for oversight of condition approval studies.

Next slide.

So based on these results and based on an ongoing pilot we had of epidemiologists involved with PMA reviews we decided there was need for a change. And the goal for that change basically focused on the following:

To obtain useful, timely and quality postmarket information on the safety and effectiveness of devices as they move into the marketplace;

To better characterize the risk and benefit profile of these devices. For instances, their long term performance, and to add to our ability to make sound scientific decisions based on these timely and high quality studies.

So what did we do in terms of change? The next two slides speaks to this. We
transferred the condition of approval study program from our premarket side of the house, the Office of Device Evaluation, to our postmarket side of the house, the Office of Surveillance and Biometrics. We did that effective January of this year.

We did that for two reasons. One, our office has the resources to oversee the program and we also have the resident expertise in epidemiologists to be part of this program.

We developed and instituted an automatic tracking system for these studies so we could acknowledge receipt of the protocols and interim study reports, and follow-up when reports were not received.

Next slide.

Most importantly, we added epidemiologist to all the PMA review teams for all the five review divisions within the Office of Device Evaluation. The epidemiologists were tasked with the development of postmarketing monitoring plans during the premarket review. These plans spoke to the best means of monitoring the safety of these products in the postmarket period.

Epidemiologists assumed the lead in developing and formulating postmarket questions, the lead in the design of condition approval study protocols and tracking those study results over the period of the study. And throughout this process we collaborated very closely with all members of the PMA review team.

Next slide.
In addition, we addressed motivation for study conduct, meaning how best can industry do these studies and how best can FDA participate in these studies. And first and foremost, obviously it's important to address the important postmarket questions: What are the essential questions that need to be addressed in these condition approval studies and to develop a good study protocol to address those questions and objectives.

We had to acknowledge the receipt of these protocols and study reports in real time, providing real time feedback to the industry.

As part of a guidance document we hope to issue soon, we hope to be transparent with regard to these studies by posting the status of these studies on CDRH's website.

And lastly, there are other authorities that we can levy if companies do not perform these studies with due diligence. And those other authorities give us leeway in terms of misbanding the product or levying monetary penalties if the companies continue to fail to do those studies.

Next slide.

And lastly, what's the impact on the Advisory Panel? We will attempt to lay out the important post approval public health questions for the Panel's deliberation and possible considerations. And we will also inform the panel, that is FDA and industry, on a periodic basis about the results of these studies that were approved.

Thank you very much.
EXECUTIVE SECRETARY COLBURN: Thank you, Dr. Gross.

Before I turn the meeting back over to Dr. Edmiston, I'd like to ask that all cell phones and pagers be turned off or placed in the silent mode, please, so they do not interrupt the business during the time of this meeting.

Dr. Edmiston?

CHAIRMAN EDMISTON: Thank you.

At this time we have several presentations from representatives of the Division of Anesthesiology, General Hospital Infection Control and Dental Devices.

Our first presenter will be Mr. Lin, Director of the Division of Anesthesiology, General Hospital Infection Control and Dental Devices. He will provide a very brief update of the Division's activities.

Dr. Lin?

DR. LIN: Good morning.

I thought I will spend a few minutes to talk about what the current update. I know that since the last Panel meeting the Division has changed significantly. So I will spend a few minutes to talk about what the Division, and following my presentation the two branch chiefs are going to give you an update what each branch chief's activities.

As you probably may know, the Center for Device and Radiological Health composed of at least six office, and because of the time I don't want to go into the detail, but next slide, please.
Office of Device Evaluation, where that's most of us work in the Office of Device Evaluation, is composed of five divisions. And division is divide according to product line that we are responsible for reviewing. And the divisions of Anesthesia, General Hospital and Infection Control and Dental Device are one of those divisions in the Office of Device Evaluations.

Next one.

Currently the Division has myself is Division Director. And then we have Dr. Ginette Michaud who is sitting in the audience. Dr. Michaud, can you -- she's my Deputy Director.

Next.

From the Division's name imply that we are responsible for four product lines. One is the Anesthesiology and Respiratory Device branch. And at current the branch chief is Ms. Ann Graham. And some of you probably already met. We have a panel meeting not long ago.

And then we have a Dental Device branch, and the chair of the branch is Dr. Susan Runner. Some probably also met. We also had panel meeting a few months ago.

And then the General Hospital Device branch is headed by Mr. Tony Watson. Is right here.

And Infection Control Device branch is headed by Dr. Sheila Murphey. Is right here.

Next. And the FDA's, our divisions for your information we have three major panel involved with our product lines. First one is Anesthesiology and Respiratory Device Panel. And
the second one is Dental Product Panel. And the third one is what we are here now, that's General Hospital and Personal Use Devices Panel, which is here by General Hospital Device branch and Infection Control Device branch.

And Dr. Murphey is going to give you an update what Infection Control Devices activity.

Thank you.

DR. MURPHEY: Good morning. I'm Dr. Sheila Murphey, the branch chief for the Infection Control Devices Branch.

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Our branch has a number of scientific reviewers with different backgrounds. We currently have three microbiologists, that will be four in two weeks. We have just filled the open position mentioned.

We have a biochemist, a nurse and a biologist. We also have a fellow whom we share with OSEL, whom we will have for another two months.

My own background is clinical infectious disease and hospital infection control.

Next slide.

Our branch reviews a number of devices. We fall into two major categories. We look at everything related to sterilization. All types of sterilizers, the medical washers, washer disinfectors and endoscope washer disinfectors.

We also review high level disinfectants and liquid sterilants.
We are responsible for looking at the reprocessing of single use medical devices. We look at the sterilization packaging systems and the indicators to indicate the adequacy of the sterilization process.

We also review personal protective equipment; gloves, gowns, masks and such devices.

We also are responsible for reviewing needle disposal units and needle destruction devices, which are PMA devices.

Next slide, please.

Recently published guidance documents for our branch include the Guidance for Industry and FDA Medical User Fee and Modernization Act of 2002, The Validation Data in Premarket Notification Submissions For Reprocessing Single Use Devices. This is a preliminary document. There is work underway for a final guidance document. Also the Premarket Approval Applications for Absorbable Powders for Lubricating a Surgeon's Glove, the Surgical Mask Guidance, the Submissions for Chemical Indicators Guidance.

Next slide, please.

We have several new guidance documents in progress. The one that we hope will be available soon will be one addressing antimicrobial agents on medical devices.

We are working on a guidance document for the reprocessing of single use medical devices and also one for standardizing the reprocessing of reusable devices. This will concentrate particularly on cleaning devices.
We have a guidance document in progress for the germicides for reprocessing reusable hemodialyzer systems.

May I have the next slide?

We are also working on revisions to existing guidance documents, the one that covers surgical gowns and drapes, the one that address chemotherapy gloves, medical sterilization packaging systems. Another for needle disposal devices and biological indicators.

Can I have the next slide, please?

Review challenges for our division relate to the technology that we review. Nontraditional sterilization technology is a fascinating new area. There's a great deal of new technology coming along, and validating the processes involved can be challenging.

The reprocessing of single use medical devices is progressing. We are seeing increasingly complex devices being submitted for reprocessing, the validation of this is a very complex process, as is the need for standardization among the entities conducting the reprocessing of single use medical devices.

And finally, the cleaning of medical devices, a general topic which addresses not just single use medical devices but really all medical devices, is something that needs validation and more standardization we believe throughout the industry.

Thank you very much.

EXECUTIVE SECRETARY COLBURN: Thank you.
Next we have Mr. Anthony Watson, Chief of the General Hospital Devices Branch who will give a brief update on the FDA General Hospital Device activities related to this Panel.

MR. WATSON: Good morning. My name is Anthony Watson. As mentioned, I am the Chief of the General Hospital Devices Branch, and I'm going to give you an update on what has happened in our branch since the last Panel meeting.

Just to give you some idea of my background, I'm a general engineer. I've been with the FDA for a little over 11 years. I was a reviewer in another branch for 10 years and I took over this branch in spring of last year.

This Panel last met August 2, 1999 and two guidance were discussed at that Panel meeting, one for pen injectors and one for jet injectors. Obviously, jet injectors are the topic of today. In particular, during that discussion six years ago there was quite a bit of discussion regarding cross contamination of jet injectors. And that is actually going to be the focus for today's meeting.

As you might imagine, in six years there's some degree of turnover. This branch has had a significant amount of turnover. As I mentioned, I became the branch chief last year, March of 2004. Our branch right now consists of seven members with varying backgrounds. We have three nurses, three engineers of different backgrounds, different types. And we have one microbiologist.
We have in our branch a lot of devices that have broad uses. As our name implies, General Hospital, we have general use devices, needle-free, obviously jet injectors as we're going to talk about them today and well as pen injectors. We do both implantable and external infusion pumps, syringes and needles and IV admin sets, and long term and short term intravascular catheters.

In addition to that, we also do devices that have sharps injury protection features. These differ from the devices that Dr. Murphey's group reviews in the fact that they deal with them after they are used, and these devices actually incorporate sharps injury protection features.

And one area that's really growing for us is the general use medical software area. We're starting to see a lot more action in this particular area.

We also review acupuncture needles, pharmacy compounding devices. And we deal quite heavily with combination products. Those are products that have devices and either a combination of biologics or drugs.

We've also published a number of guidance documents. In 2001 we published a Class C Special Control Guidance document for Pharmacy Compounding Systems. And that was also concordant with the actual classification of those products.

We put out a guidance document in 2002 for sharps injury prevention features,
which we are presenting in the process of updating.

And in 2004 we cleared an interesting device, implantable radio frequency transponder system for patient identification, health information. And in accordance with that process we also generated a Class II special control guidance document.

The last, the most recent guidance document that was published was intravascular admin set. This is a revision to an existing guidance document. And that was published in April of this year.

We are in the process, we have quite a bit of guidance documents that have been around for a while. And we are in the process of updating some and actually generating some new guidance documents.

The pen injector and jet injector, as I mentioned earlier, six years ago we had a discussion about what kind of information would go into those guidance documents. We're now going to be actually generating those guidance documents. And we're going to be revising our guidance documents to infusion pumps, intravascular catheters and pharmacy compounding devices.

We've had a number of clearances over the years that have some interesting issues and features associated with them. But perhaps the one that's generated the most interest was this implantable radio frequency transponder system for patient identification and health
information. And it's significant in a number of ways.

First of all, just to briefly describe the device, the device really consists of three components. A chip that's implanted in the skin that's about the size of a grain of rice, an introducer which is used to implant the device and a reader. The reader actually -- the device itself, the chip only contains a patient identification number. It doesn't contain any other information about the patient. But the reader can extract that code, then using that code whoever is authorized to go into a proprietary database can then take that information and pull up the patient's information. That health information is supplied by the patient. It is generated from any other location. So the patient actually gets to tell the person what they want the person to know.

That device was cleared under the de novo review process, and it was really -- I was real proud of the review team because it was really a cross cutting kind of product. We had people that looked at the electromagnetic compatibility of the product, the bio compatibility of the product. The MRI compatibility of the product. There was software discussions about data security, data integrity.


The bottom line was it was under a de novo review process, which is a process that's
beyond the scope of me describing it at this Panel meeting, but it required us to do all that within 60 days and generate a Class II guidance document as well. So I was real proud of the review team for that. And you may hear more about this product.

    Next slide, please.

    We have a number of challenges that we're facing in our branch. And I have combination products up there because they're always a challenge.

    Inter-center consults, getting consults with other centers to review them in our statutory time frames is always a challenge. Our other centers have been great for helping us with that, but it is a very difficult thing to do.

    Cross-labeling of combination products. There's always a question whether the device component should reference the drug or biologic component and vice versa, how much of that should occur. We're always dealing with that.

    And, as I mentioned, the growing area for us is software based devices. One of the things that really is a challenge is that these devices we're talking about a lot of times are just software. There is no hardware associated with them. We're talking code, maybe put on a CD, a DVD, placed on a server, something like that. And how do you regulate that? What performance do you look for? I mean, what are the issues associated with that?
And we're also dealing with a number of existing devices that have IT technology applied to them, particularly in the area of wireless communication through networks. And where does the device begin and where does the device end? That's always a question there. But we are seeing more action in that area.

Human factors: This one is basically related to our attempts to address human errors due to human factors. Particularly in the area of infusion pumps, there's always a question about whether these errors can be prevented through proper human factors, considerations and the design process. So we're really starting to emphasize that in our review process. And it's not just infusion pumps, it's really any device that we deal with that has a high human machine interface. We want to make sure that we're asking those people to look at those human factors in the review process at the design stage.

And one area that's really sort of exploded for us recently is the use of -- I have peripheral catheters up, but we're also talking central catheters as well that are using power injection for contrast media.

Obviously these type of procedures generate high pressures, high flow rates. A lot of catheters on the market are not actually tested to that level. And we want to make sure that we've got the proper testing for that. That's a challenge because these devices are made with different materials, different sizes. No two are alike, basically. So we're trying to
develop testing for that, is really a challenge for us. But we do have some great ground work. Our reviewers have done a good job about identifying the clinical issues and taking a look at the engineering aspects.

And one other aspect that we are really concerned about is what information do we need to provide for users. It's really critical that the users know how to incorporate that in the way they're using the products.

So that's the General Hospital Devices update. And thank you very much.

CHAIRMAN EDMISTON: Thank you.

We will now proceed with the first of our two half hour open public hearing sessions. The second open public hearing session will follow the Panel discussion this afternoon.

During this period public attendees are given an opportunity to address the Panel to present data or views relevant to the Panel's activities. Some individuals have already given advance notice of wishing to address the Panel. Each speaker will be given a 15 minute opportunity to speak.

I would like to remind the public observers at this time that while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the Chair.

We would also ask at this time that persons addressing the Panel come forward, keeping in mind this presentation is being transcribed and speak clearly into the microphone.
If you have a hard copy of your presentation, please provide that to my colleague, Lieutenant Colburn or leave it on the transcription desk.

The following statement is to be read verbatim at the general matters meeting. "Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting the FDA believes that it is important to understand the context of the individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral comment to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting.

For example, this financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationship.

If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking."

At this time I believe we have two speakers. We have a Mr. Hooks and a Mr. Weidman, is that correct? Please come forward and
introduce yourself. At this time indicate your affiliation.

Each speaker is allotted a 15 minute period.

MR. HOOKS: Good morning.

I don't have any financial things with anybody, nobody paid for my way.

What we'd like to do is address the military application for aspects of the jet gun injectors.

I represent HCVets.com. It's a website.

Go to the next one. All right. I'm getting ahead of myself.

Anyway, what we do is we have a website that allows veterans, military members, their families or whatever to seek information on the contamination or infection of hepatitis C via the jet guns.

If you look at this chart here you'll see that the majority of the people that have hepatitis C are veterans, the largest portion of Vietnam era. The reason that occurred is if you think about the military at the time, was probably at their peak. The one thing we all share in common is we were all inoculated with the jet guns.

The other thing is when you look at most of the studies referring to this stuff you'll see they mention hepatitis B and HIV. Well, hepatitis C is more infectious than HIV, it's also a lot harder. It's a lot harder to get rid. So the cleaning and all like that is very important.
If you look at the VA Administration and all like that statistics, there's 25 million plus veterans still alive in this country. Only about ten percent of these folks go to the VA. So the numbers that you're going to see are smaller, I believe, because there are a lot of veterans who do not use the Veterans Administration as their health service.

If you look at the numbers from the CDC and the Veterans Administration right now, out of the 25 or so, comes out to about 458,000 veterans have hepatitis C. But I think the numbers would be quite larger than that if you took into account the whole population.

If you take the numbers in with all, add the 2 percent and everything like that for the population, of course there's really been no studies on this since '94, so these numbers were taken with the CDC at different times and all, and the 2 percent was added, you know, for the population growth and stuff like that. And you come up with these numbers here. Out of the 33.4 million veterans or people that are infected with hepatitis C, 2.2 million would be veterans.

Based on the infection rates quoted by the VA and the CDC, approximately 75 percent of the estimated people with hepatitis C are military veterans with infections longer than 20 years. Out of the estimated 3 million chronically infected stated by the National Institutes of Health, an estimated 2.2 million
had this disease for over 20 years, a projected 20 percent or 450,000 veterans are expected to develop sclerosis or 90,000 are expected to develop cancer now.

Next one, please.

I'm sorry about the picture. It didn't come up. It was a graph.

The role of the jet gun in the transmission of hepatitis C. The Ped-O-Jet was introduced about 1950s, developed under a U.S. military contract for mass vaccinations of recruits of 600 to 1,000 injections per hour. The WHO document says an hour and a half.

If you go on an hourly basis, that's about six injections at 600 or 3.6 injections a second per hour. If you go to an hour and a half, it's 9 seconds per injection or 5.4 injections per second. That's a relatively rapid fire. I think anybody's that's been around in those lines understand there's no time to waste. Real close quarters and you're hustled through.

Next one, please.

This is a picture of the old apparatus that was used. I believe up until about '94. It wasn't me.

Okay. Next one, please.

The Air Force Infectious Disease and Control Epidemiology Board, Department of Defense Wide Review of Vaccine Policies and Procedures said that injector nozzles were frequently contaminated with blood. What they did is they had -- I think it was probably a surprise visit to Parris Island. And they
witnessed a mass injection of a lot of recruits coming in. And they noted in that document that there the nozzles were frequently contaminated with blood. There were no wiping or precautions taken.

Next one, please.

The problem with the jet injector gun during the Board meeting in 1986, Captain Michael Stek, Jr., MC, USN presented data and press clippings to suggest that contamination of the jet injector gun which had been used in a private clinic in California in 1985 was responsible for causing hepatitis in 64 patients. The possibility was also raised that HIV infection might be transmitted by the jet gun when biological products such as gamma globulin were administered. In numerous meetings the board recommended in 1988 that an injector gun be used only by authorized military and technical parts and sterilized according to standard procedures.

Next one, please.

What are the standard procedures for the jet injections?

Next one, please.

That would the manufacturer's recommendations.

Next.

The manufacturer's recommendations recommended the devices be wiped in between each injection. There was a meeting, I guess, of this organization in '99 where a representative of the company was here and they stated that in
35 years they were always wiped and never had an issue.

I'd like to bring out at this point in time probably you never had an issue with hepatitis C by the simple fact a majority of people are asymptomatic and it takes decades before you find out you've got a problem. Thirty-five years is not a stretch in this area. The majority of the people won't have a problem until at this point in time.

There was a study done in England where it came out that they could infect 31 out of a 100 if the guns weren't wiped. There was a statement made that there's nowhere in the world recorded that the guns weren't wiped.

Well, we have -- the next one, please.

The website did a survey, and this a partial selection of people that answered the survey. We have answers from medics that administered the shots and received the shots, we have all different bases and military branches, and comments from the individuals that state the guns were not wiped. I personally can attest to that. They didn't wipe them before they nailed me or anybody before or after me.

Next one, please.

The expectations fell short. As I stated earlier the people in charge of the basis and the medical, and stuff like that, were under the idea that the guns were being wiped in between each injection. That's not the case. The human error factor, for whatever reason, the things weren't followed. I've talked to some
medics that had this duty when they were in the military, and this is what they considered to be a great job. You go in in the morning, you throw a bunch of shots out, you get done early. You got the rest of the day off. You know, that was just the way they looked at it. There was no harm, no fault in my mind because they had no idea with the little bit of training they had what they were doing. They had no understanding of the infection rates. Hepatitis C at the time wasn't even something described. You were non-A, non-B if you were diagnosed at all.

The next one, please.

In dealing with the VA, it's been an uphill battle for a lot of folks because the simple fact is they don't fit into the prescribed methods of transmission for hepatitis C. The CDC and all have kind of left out a whole generation of folks, and it makes extremely hard for someone who has no other reason except for their injections, to get hepatitis C.

Back in 2003 there was a claim that was based solely on the jet injectors. The veteran won that one, but it had to go to Cleveland to the Tiger Team to get there.

Next one, please.

Here's some of the documentation that was used and the studies that were used to validate the claim.

I'd like to mention, too, besides the hard copies, I have CDs that if you go on line the links will work and link you to these studies. It would take too long to get into them.
Next one, please.

This is the DoD's needle-free injection policy chronologically. It shows when they started to stop using the jet injectors and the reasons why. The dates and the organizations, and their orders that came out. Once again, you know, the links will take you to the full study.

Next one, please.

Okay. For infection rates we're talking picoliters of blood, that's very small. It doesn't take a lot. And there's been numerous studies on that.

Hepatitis B, basically, can be transmitted at about 10 picoliters. Hepatitis C runs in, I believe, at about 35 or HIV at about 40. Somewhere in that range. There hasn't really been any hard studies that I've seen, or found or heard about that relates to hepatitis C. That's something that really, really needs to be looked at because it's not a problem that's going way. I mean, this whole thing with me not knowing that I was infected, I in turn infected my wife. She wasn't real happy about that, but I'm not the only one that has done that not knowing. I've donated blood up until like '92, and then I stopped for physical reasons not because I was tested with hepatitis C. So we have a larger epidemic then what's showing up in the numbers. And it really needs to be looked at. We have to stop it any way we can. And by ensuring that these guns or any other device that has the ability to transfer blood in any amount is designed in a fashion that can't
happen. I don't want anybody else to have to go through what I've been through, or a bunch of other fellows, either.

Next one, please.

This is a CIA report, which once again the link will take you to. What we have here, basically they did a study in the areas of the sub-Sierra and Southeast Asia, and stuff like that. They had an upheaval with HIV, and all like that.

The other problem you'll see and where our folks are right now serving us with great courage, they're also hot beds for hepatitis C. I think that the fellas and gals that are over there now should be checked. If they've had any injections and stuff, they should also be checked and nip in the bud before it gets like it did with us 20/30 years down the road.

Next one, please.

Once again, this study is taken not in this country, we really haven't taken the time to do in depth studies for hepatitis C. We have some on HIV and some on hepatitis B. So most of the studies you'll see are from foreign lands. We haven't really addressed it appropriately.

Next slide, please.

That's my idea of the beautiful world and all reality. Like I said, any device that transfers blood, the needle jets specifically, they need to be addressed appropriately. I know there are some modifications that have been made like caps and disposable ends and stuff like
that. I've seen where they're working on things. But they really do need to make sure these things don't transmit blood in any fashion.

That's all I have.

CHAIRMAN EDMISTON: Thank you very much, Mr. Hooks.

MR. HOOKS: Thank you.

CHAIRMAN EDMISTON: At this time I'd like to invite members of the Panel who may have questions or clarifications of Mr. Hooks' presentation to please address the speaker. Are there any questions from members of the Panel?

Thank you very much.

Do we have any other speakers who wish to address the meeting?

I think at this time since we're ahead of the game here, we're going to go ahead and take a brief 15 minute break. The next presentations will be from the FDA, and there's a continuity of those presentations so I'd rather not break them up.

So let's take a 15 minute break and convene at 9:15.

(Whereupon, at 9:00 a.m. a recess until 9:17 a.m.)

CHAIRMAN EDMISTON: I think we'll reconvene the meeting now. I'd like to ask all the Panel members to take their seats, please.

I'd like to make a very brief announcement. It was initially announced that Dr. Weniger from the Centers of Disease Control would be here giving a presentation. But,
unfortunately, he will not be able to be here to make that presentation.

We will now proceed to the FDA presentations for the Panel. The first speaker will be Mr. Anthony Watson, Chief of the General Hospital and Personal Use Devices Panel. Mr. Watson?

MR. WATSON: Thank you. And I'm just going to introduce the speakers. We have three speakers today.

Mr. Jason Lipman is an engineer in the General Hospital Devices branch. He will be discussing the regulatory history of jet injectors.

Then we have Dr. Shewit Bezabeh, who is a medical officer in our division. And he will discuss the safety history with these devices.

And then following him will be Dr. Daya Ranamukha, who is a microbiologist. Is that correct? Molecular biologist. I apologize. A molecular biologist from our Office of Science and Engineering Laboratories. And he will discuss potential methods for testing for these devices.

So now I'd like to ask Mr. Jason Lipman to come to the podium, please.

MR. LIPMAN: Good morning. My name is Jason Lipman. I'm reviewer in the General Hospital Devices Branch. If you haven't figured it out yet, we're here to talk about jet injectors.

CHAIRMAN EDMISTON: Excuse me. Could I ask you to speak directly into the microphone.
MR. LIPMAN: Oh, sorry.
CHAIRMAN EDMISTON: We're having some problem hearing you.
MR. LIPMAN: Is that better?
CHAIRMAN EDMISTON: Yes. That's great.

MR. LIPMAN: Okay. Jet injectors are also known as needle-free or needleless injectors. As defined by the Code of Federal Regulations a jet injector is a nonelectrically powered device used by a health care provider to give a hypodermic injection by means of a narrow, high velocity jet of fluid which can penetrate the surface of the skin and deliver fluid to the body.

Next, please.
Jet injectors are Class II devices. They regulated through the 5.10(k) premarket notification process. And jet injectors must demonstrate substantial equivalence.

Next, please.
There are two main types of jet injectors. There are single use devices and there are multiple use devices.

Single use devices are devices in which the entire device is discarded after one use.

There are three types of multiple use devices. There's single use cartridge devices in which the fluid contacting components are discarded after one use. There are devices that are labeled and sold for only one patient. These devices can be multiple use, but only one patient is using them. And there are devices
that have a reusable fluid path. As indicated by the yellow, these are the devices that we will be focusing on today. These devices typically have a large medicinal vial that fills an injection chamber after each subsequent injection. Reusable fluid path injectors are also known as multi-Use Nozzle Jet injectors or MUNJIs, for short.

Here's a picture of a bunch of jet injectors. As you can see, many of them do have that medicinal vial at the top of the injector which I just mentioned.

Next, please.

I want to talk a little bit about how a jet injector works. Jet injectors must create high pressure, usually by the use of springs or compressive gas. This high pressure forces the medicinal product out of an injection chamber through an orifice and into the body.

There are four target tissues for injectors; mucosal membranes, dermal tissue, subcutaneous tissue, intramuscular tissue.

Next.

There are two primary uses for MUNJIs. That's immunization and administering anesthesia during dental procedures.

There are several advantages of MUNJIs use. They include high delivery rates. It doesn't take very long to prepare for a subsequent injection.

There are several needle-free benefits for MUNJIs use. There's no reuse of needles, no chance of contaminating needle-stick
injuries. And there's no patient fear of needles because there, obviously, is no needle.

There's a reduction of volume of clinical waste.

And these devices are economical because the device is reused.

There are a couple of disadvantages for MUNJIs. The focus of our presentation today is the first one, the potential for blood cross-contamination or disease transmission.

The second is the potential for laceration injury from improper technique. And this can occur since the jet stream has such a high velocity of jet stream that if you were to actually lift it off the skin prematurely, you could lacerate the skin from that high velocity jet.

Next, please.

There has been one documented case of cross-contamination. This was in California in 1985 at a weight loss clinic. It resulted in a hepatitis B outbreak. In addition to that outbreak, there have been in vivo animal studies and bench laboratory studies that also link these devices to disease transmission. This will be talked about in more detail by subsequent presenters.

So I want to talk about how the cross-contamination occur. It can occur, as we heard before, about blood actually the skin contacting surface on the injector or that blood or serum can actually go up into the fluid path. And there a couple of theories as to how that can actually occur.
One is splash-back. Again, the high velocity jet can actually bounce back off the body and back through the small orifice. Or there's also a thought that the injection, the pocket of fluid in the body is pressurized and pressurizes the tissues around it and those tissues can actually push on the fluid and push back up through the orifice.

In either way, the residual infected blood or serum can be injected into the subsequent patient causing a blood-born illness.

Manufacturers have attempted to mitigate that risk of cross-contamination. The primary design of the mitigations are single-use patient contacting components, such as caps, spacers or sheaths. But there have been no validated methods to assess the effectiveness of these components.

Next, please.

So the challenge of evaluating the potential for disease transmission exists because there's no consensus on the amount of blood contamination that can potentially transmit disease, and there's no validated test method for detecting blood cross-contamination. And, again, this will be talked about in more detail in subsequent presentations.

There is global concern about using these devices, the new devices as well, the new MUNJIs. The World Health Organization recommends against MUNJIs use. The Centers for Disease Control and Prevention recommend weighing the risks versus the benefits; the risks of typical syringes and needles versus the
jet injectors. Hopefully, I'm hoping that Dr. Martin Friede will talk in a little bit more detail about their current policies.

In 1999 the FDA held an Advisory Panel meeting to discuss the guidance for jet injectors. This was talked about earlier today. This was to figure out the evaluation criteria that would be documented in our guidance document for evaluating jet injectors. During this Panel presentation, or this Panel meeting we also discussed the potential for cross-contamination, what we're here to talk about today.

At the end of that meeting there were two recommendations made by the Advisory Panel to the FDA relating to this issue. The first was to consider the postmarket surveillance. We have reviewed all of the medical device reports on this issue. There has only been one medical device report related to cross-contamination, and this was actually a case of misuse and did not result in any blood-born disease, at least documented blood-born disease.

Could you go back for a second? Thank you.

The second recommendation to the FDA was to investigate the possibility of developing a standardized methodology to determine contamination. We have reviewed all the current methods and even looked at some future methods, and we will be talking about this more later today. But to date there are no validates test methodologies available.

Next, please.
These are the references that I've cited in this presentation.

Next, please.

I just want to talk a little bit about the purpose of today's meeting. We're here to discuss the cross-contamination risk associated with MUNJIs and to discuss the methods that might be used to assess this risk.

This concludes my presentation. I hope it gave you a good background for what we're going to discuss today.

At this time I'd like to call up Dr. Shewit Bezabeh who will give a clinical perspective on this issue.

Thank you.

DR. BEZABEH: Good morning. My name is Shewit Bezabeh. I'm a Medical Officer with CHRH, the FDA.

My background is both public health and epidemiologist. Also I'm an internist. I'm also active in a clinical practice. I have been with the FDA for the past four years as a Medical Officer.

Next slide, please.

Today I will give you an overview of MUNJIs. The device has history. The public has need. The effectiveness experience with these devices, the history of safety concerns and the concerns for current use.

Next slide, please.

Jet injectors are needle-free delivery devices that facilitate the administration of medications under high pressure stream into tissue. These devices can
administer vaccines and other medications into subcutaneous tissue, intramuscular tissue and also dermal tissue.

People have categorized these devices into three categories. The first one, the first one I'll use is usually used for single use can also be reused with the same person. We see these devices being used with a number of diabetics.

The second category is low work load. About 30 injections per health care worker.

And the third category, which is the focus of today's meeting, will be high work load, injection of a 100 injections per health care worker.

Next slide, please.

The history of these devices, they start in the 1860s, was initially developed in France to administer a number of liquids.

In 1936 the first jet injection device was attempted in New Jersey.

In the '40s the first commercially available jet injector was Hypospray. It was initially devoted for single use, self administration for diabetics. It was designed to overcome childhood needle phobias.

From the mid-'40s to the '60s it was introduced massively into the military for clinical use.

From 1976 to present up to now it is cleared by the FDA as a Class II pre-amendment medical device.

The need for public health for these devices is multiple -- for a number of reasons.
These devices are needle-free, so they avoid the needle entrance risk due to needle injuries.

Globally there's high risk with needles and syringes because of improper recycling, and also reuse with proper sterilization. WHO experience with that, half of the injections in the developing world are unsafe and result in about from 8 to 16 million hepatitis B virus infections per year, 2.3 to 4.7 million hepatitis C infections and about 100,000 HIV infections.

In the U.S. there are about 87 health care workers contract hepatitis B virus due to occupational exposure, of this there's about 200 cases per year.

The risk of infection after a needle stick injury with an infected blood for HIV is about 3 in a 1,000, hepatitis C the range was from 1 to 7 percent and hepatitis B, which is the most highly infectious, about 30 percent.

The other aspect of need for these devices, they can be used in response to bioterrorism because they can rapidly immunize first responders, exposed populations. They can be used in pandemics, regional epidemics and emerging infections. They have been used with meningococcal meningitis, yellow fever, influenza.

There is a global need for this eradication. They have been used with polio initially. Polio is almost eradicated. Measles is targeted for eradication. Many of the program for immunization vaccines practices require injections. And also as mentioned
earlier, needles and syringes have a number of limitations.

They also have potential need for future newer vaccines. They have been tested for malaria DNA vaccines and also for emerging vaccines such as when the vaccine is available for SARS and other infections.

The advantage of this device is included, it has a potential high rate of vaccination. They can vaccinate over 600 people per hour. Can respond to pandemics, regional and local epidemics. Can also respond rapidly to bioterrorist attack. Can administer off-the-shelf vaccines.

They have a long history of use with many types of vaccines. They can be filled at the end user or by a manufacturer. They eliminate the needle stick risk and sharp disposal burden. They are also very cost effective compared to needles and syringes.

The main disadvantage, which is the focus of today's meeting, is the potential for blood cross-contamination. Also, they're believed to have increased pain, especially the adjuvant added vaccines as compared to needles to syringes. Also, improper technique may result in laceration of injury. They're believed also more reactogenic than needles and syringes. You've seen increased erythema hematoma bleeding at the injection site.

Immediately you see more erythema and hematoma. Some of the delayed reactions includes soreness, erythema in duration and edema. Other local adverse events include
bleeding of injection site. As mentioned earlier, there could be laceration, especially if improper technique is used. And there have been very rare reports of traumatic injuries.

In terms of effectiveness expense. We have over 50 years of device use delivering millions of injections. There have been a number of studies which demonstrate effectiveness of these devices, mainly by measuring immune response and immunogenicity. We have a number of randomized control trials, review of clinical trials. Also respected comparative studies.

I should note that even though these studies assess the effectiveness of these devices, none of them have studied for their safety.

In terms of past use, the U.S. Department of Defense from 1965 to 1980 have given about 20 to 40 million injections to military personnel. The global smallpox eradication program, 50 to 100 million. During 1976 swine flu epidemic, about 75 million have received vaccination using the device. The African Meningitis Program, 1988 through 1998, about 80 million. The Brazilian Measles Eradication Program, an estimated 60 to 80 million people have received vaccination with this device. And globally, from 100 to 500 million have used this device to receive vaccinations in the past 30 years.

Even though we have extensive history of use and effectively, there have never been no
surveillance implemented to assess transmission potential between this use.

Next slide.

Some of the vaccines that have been used with this device, include both light and inactivated vaccines, measles, mumps, rubella, yellow fever. Some of the inactivated vaccines include botulism, cholera, hepatitis A and B, influenza and others.

Next slide.

In terms of the history of safety concerns, in the late '60s early '70s people started noticing blood on the nozzle of these devices which was initial concern for the purpose.

There was only one documented disease transmission which occurred in California in 1985. A cohort of patients were receiving formal injections, had clearly documented hepatitis B virus. We believe this transmission was through this device.

In addition, we have some experimental evidence as well as some epidemiologic evidence implicating this device, this is transmission. Some of the experimental evidence include in 1985 Brink coworkers took mice which were clinically infected with LDH virus. They had a cohort of mice received injection and they were able to demonstrate that 16 out of 49 mice had acquired LDH virus through that injection.

In 1988 Zachoval, which have reported in the *Lancet*, took 5 patients. Four of them had positive serologic markers for hepatitis B. The
fifth patient was HIV positive. They injected them with a jet injection device and then they tested the nozzle and the injection site. While the nozzle was negative for any markers, three out of four of the hepatitis B carriers, the injection site was positive for hepatitis markers and the HIV patient also positive for the marker. The theory being that if there had been a subsequent injection, these markers would have been transmitted to the next patient.

Next slide, please.

Some of the epidemiical evidence so far include the 1994 about 2800 subjects were receiving routine immunization via jet injector. The injected was tested instead of giving it to the next subject, it was tested. It was collected in a test tube and tested for blood. And about 28 of them, which is about one percent of the subject recipients tested for occult blood.

In 2001 there was an epidemiological survey done in Brazil where about 750 patients where hepatitis B virus carriers had a multi-variant analysis to evaluate the risk factor for transmission. And out of the multi-variante analysis, a cohort of people who had received prior yellow fever vaccination via the jet injector was a risk factor as for hepatitis B infection. Again, implicating the device as a vector for disease transmission.

A field study done in Brazil again to look at the safety of the injector. This investigator took two modes of injection type. One they took noncompliant stimulating no
interference between the device -- I mean, vaccine delivery. And the second mode was a confirmed compliance mode where the nozzle of the device was swabbed with alcohol. And they took the volunteers and injected them with buffered saline and they collected three subsequent injected into a test tube and tested the ejected for blood.

In the first injection in the noncompliant mode, about 30 out of 117 patients, which is about 11 percent, were positive for occult blood. And then in the compliant mode, 9 out of 117 patient, which was about 8 percent, was positive for blood.

In the second injected, about 4 percent, 4 out of 117 in the noncompliant mode. And the second mode, the complaint mode, 3 out of 117, which is 2.5 percent were positive for blood.

Whereas, the third injected there was no blood positivity.

Again, even with interference alcohol swab, as you can see both the first and second injected in both the noncompliant and compliant mode there was blood positivity. Again, implicating that this device possibly delivers transmission.

In 1999 the Armed Forces Epidemiology Board observed frequent blood contamination of the nozzle in high volume recruit immunization.

Next slide.

Based on this and other safety concerns and other studies, a number of agencies come up with policies. In 1987 WHO restricted
device use. In 1996 WHO also stated that MUNJIs is not recommended for mass use. In 1997 the U.S. military withdrew the use of the device. In 1999 FDA had a Panel presentation meeting, as mentioned earlier. And the Panel meeting was to discuss a guidance document. However, also the safety of this device were discussed. And the Panel had two recommendations. The first recommendation was to continue to do postmarket device surveillance. And the second recommendation was to investigate the possibility of developing a standardized methodology for the safety of the devices.

In 2002 the CDC Advisory Committee for Immunization Policies discussed the use of these devices and they stated that MUNJIs use should be limited weighing the risk versus benefit of MUNJIs with needles and syringes.

And most recently, 2004, WHO had also discussed the use of these devices. And the conclusion was it would not be possible to adequately endorse the safety of these devices.

Next slide.

In terms of blood-born transmission, we know that hepatitis B virus is more infectious than HIV and hepatitis C. And we also know that there about 9 to 10 to 11 hepatitis B virus DNA copies per cc, which is about 1 to 100 hepatitis B particles per picoliter. There have been studies where they have estimated that 10 picoliters being the smallest amount for transmission of hepatitis B virus.

Next slide.
A number of assays have been tested and tried in the past to measure the blood injected as a marker for assay. Some of the assays include serum albumin measurement as an indicator of blood. There have been sensitive ELISA assays. However, there is no acceptable limit of blood detection to demonstrate safety of these devices. Some of the proposals which have put forward include to do clinical trials with hepatitis B positive population and also to test injected for hepatitis B virus by PCR. However, we're not sure if these assay models are sufficient to evaluate the safety of these devices, also are there any testing methods to assay the safety of the devices.

The next presenter, Dr. Daya Ranamukha will go further into the testing methodology and assays.

Thank you very much.

DR. RANAMUKHA: Thank you.

The title of my talk today is potential safety evaluation strategies for MUNJI devices.

I'm Daya Ranamukha-arachchi. I'm a molecular biologist at the Office of Science at the Center for Devices and Radiological Health. I have over ten years of experience in molecular methods in human genomics.

So going back to the percentage, and Dr. Bezabeh before and others talked about safety concerns for MUNJI use, and I want to stress the important points here again.

MUNJI can exert local adverse events and it could be delayed for early reactions, and
again can lead to bleeding at the injection site. These are more common in MUNJI devices than needle/syringe devices.

What I'm going to talk to you today about mainly, the risk of cross-contamination with blood. So I'm going to put forward the potential evaluation strategies in this context. Next, please.

So the first question that comes to your mind is when you think about cross-contamination, is there safe limits of blood cross-contamination? Insights into this comes from virology data. If you look at the hepatitis B carriers, they contain around 10 to the 9 to 10 to the 11 DNA copies per milliliter. If you go down in the volume, it's about 1 to 100 HBV copies per picoliter of blood. But it can also go in some carriers, they go to like 10 to the 15 DNA copies per milliliter.

And there's one study that shows HBV may be transmitted with as little as 10 picoliter of blood and using one animal model. This was published in 1984.

So when you combine these two facts, is the 10 picoliter of blood or 10 to 1,000 HBV copies the limit that we want to dictate? And then the next question is are there test methods to achieve the required limit of detection? These are the questions that we need to address.

Next, please.

So if one were to evaluate the contamination risk, what are the challenges we have to face between use cross-contamination. So these are whole list of questions that comes
to one's mind; collection of sample; how we can collect the samples to evaluate between use cross-contamination. Then what are the analytes? What are the molecular methods? Then when you think about the molecular methods, what are the limits of direction and accuracy, specificity and reproducability. And then finally depending on all these answered, what are the safe acceptance limits? Is there acceptance limit?

So addressing all these issues, I have divided my talk into three categories. First, analyze for testing. Once we collect the samples, how we can look at, what are the analytes that we need to test? Of course, blood markers and then we can think about pathogenic contaminates, what are the markers? Then what other methodologies; molecular methods available to determine contamination? Serology-based, then DNA amplification based and combined approaches including DNA hybridization technologies.

Then the third, cross-contamination study designs. We have animal models, we have human models. So we can look at all that.

So coming back to the first part of my talk, analytes. Obviously, many talk about blood cross-contamination comes to our mind the blood markers. So we can look at blood markers like abundantly available proteins such as serum albumin as surrogate marker for the presence of blood. So this has been done before actually using sensitive ELISA methods. But the disadvantages of using this serum albumin is it
can create false positives, false negatives and deduction limits. False positives in the sense that serum albumin presents in everywhere saliva and skin cells, so this can create false positives.

Then the false negatives. Under cold storage conditions serum albumin can bind to collection tubes. So then when you think about ELISA, the detection limits if very narrow. So you have to go through a series of dilutions in order to get within the dynamic range of detection.

Then with regard to blood molecules, I want to stress the point that what is the limit of detection 10 picoliter of blood. This number came from one single study using one chimpanzee. This study was not meant for actually looking at HBV transmission, but to evaluate it was methodologic paper looking at ELISA versus DNA detections. And in that what they did was they the serial disillusions of the saline, buffered saline and they found out that 10 to the minus 10 dilution they could infect one chimpanzee. But their aim, the object of the study was to evaluate how good at analyzing detecting HBV contamination.

So what I mean to say here is that this 10 picoliter blood limit is not statistically validated.

So coming to the next one, then the second class of analytes is the viral markers which has the highest contamination potential. For this, the infections come from needle stick injuries. If you look at HIV HCV, HBV, HBV has
the highest potential with 6 to 30 percent depending on the status of the contaminating blood.

Then HBV has the highest potential for transmission due to cross-contamination. Which is the most prevalent? Over 2 billion people are infected with more 350 million chronic infections based on the WHO report. Survivability is high and can be easily integrated into the host genome.

Next, please.

So last year's WHO injector safety meeting they come to consensus that HBV is an appropriate marker for determination of injector safety.

There are also certain group of advantages. If you are using HBV as an analyte, there's presence of international, WHO international standard and then availability of quality control panels. And availability of molecular assays for HBV detection.

There are internal controls, such as murine cytomegalovirus for evaluation of false positives as well as false negatives.

So all these advantages lead us to develop good test methods if you need to.

Next, please.

Now the second part of my talk is the test methods. What are the test methods available? There are a whole host of methods available based on serology, DNA amplification and combined approaches using DNA hybridization.

Now what I have summarized here in this table is the more sensitive methods with
the principle -- actually those principle technologies. Serology based uses serum antigen, surface antigen and also e antigen.

So then other methods uses HBV DNA. So the samples either serum or plasma.

Then the limits of the detection, I want you to look at the last two; real time PCR and NAT technology. NAT technology is the nucleic acid testing technology based on PCR, DNA amplification, plus DNA hybridization. So these limits of detection, I got it from published data which gives like 100 copies to 10 to the 7 and 10 to the 9 sensitivity limits of detection.

So I want to stress the point here that there's test methods available for single copy detection. If you want to look at single copy detection, there is no test methods available.

Now next slide, please.

I just wanted to put this slide because what other emerging technologies can do in this context. Obviously, nanotechnology comes into play. And there's some published studies, one for DNA detection called biobarcode DNA detection which can detect DNA at 500 zeptomolar level, which is a quality detecting all available copies in a solution. Then again, when you look at protein detection using the same technology, you can detect antigens at atomolar levels.

So these are only research tools which is published recently. These have not been validated under any diagnostic setting.
So the next slide, please.

And I want to stress this point before I move on to the next category. Molecular methods for HBV testing. Molecular methods have a lower limit of detection than conventional assays. And MUNJI cross-contamination may be investigated using HBV-NAT or Taqman assays. However, this has yet to be validated. Then there are studies to establish performance characteristics of these assays for HBV detection in MUNJI device use have not been conducted.

Next please.

Now I want to switch the gears here to talk a little bit about what are the possible study designs we can look at. This is the last part of my talk.

So we can look at animal versus clinical studies. If you look at animal studies, what advantages does it give? Provide well controlled biological uniform study designs and we can directly evaluate viral transmission potential. However, we are to take into consideration the substantial histologic differences that exist between human and animals schemes and muscle development.

So then the clinical studies, on the other hand, use the direct impact of injected device on cross-contamination in humans. Genetic variables are also taken into consideration. But it is unable to get IRB approval for direct human evaluation of viral transmission.

So next slide, please.
There's one published model, actually, using animals for evaluating cross-contamination potential of MUNJIs devices in this study which was published in 2001 in *Vaccine* by Hoffman et al. They used cows, young cows of 8 to 12 weeks and they used the same set of cows repeatedly. And what they did was instead of using the vaccine, they used a phosphate buffered saline in a buffer at .5 milliliter per dose. And then they injected to one calf and then collect the next ejectate before injecting to another one into a separate container. That's in the real world situation in an immunization program, that's the one that goes to the next person. So they collected that and then evaluate the blood markers, surrogate markers, serum albumin by sensitive analysis. And then they compared the results with negatives based on preinjection doses.

Next slide, please.

So using this same method we can think about potential clinical studies for evaluating cross-contamination. There are two types we can look at. If you are to evaluate blood cross-contamination only, we can use healthy volunteers, the number which has to be determined statistically. Then we can use the same protocol, saline injection and then collect the data after every single use.

And I want to make a note here. If you are using this device between users, we are to sterilize the device.

And then the second thing is if you want to look at the potential for HBV
transmission, we have to change the population now. We have to think HBV positive volunteers, but we can follow the same protocol.

So these procedures, actually, that I haven't proposed this but this has been discussed before by, for example, Dr. Bruce Weniger at CDC. He discussed this at Global Vaccine Research Forum in 2004 in Switzerland.

So this is all of the aspects that we have to think about when you develop a strategy. So I want to stress the points again. What are the constraints for developing a safety evaluation strategy? There are many unknowns. Only animal studies, no clinical studies other epidemiology studies. But if you look at the proposed number of HBV copies required for transmission, there's 10 picoliter maybe inaccurate. So we have to realize what is the lowest limit of detection that we want to achieve.

Then other test methods available to achieve the required limit of detection, there are test methods but what is the limit? That is the thing that we need to look at.

Then, again, one other point I want to stress here is that impact of dilution factor that has to be accounted for. If picoliter blood is the one that can transmit the HBV, can this be measured correctly when diluted in the ejected, that is one that goes into the device. So these are all the questions to ask yet.

So coming to the summary -- next slide, please. So this presentation summarizes the current available methods that can be used
to assist the safety of MUNJI devices. And we have HBV model, it's a good HBV model for evaluating the contamination. And there are test methods available, but none of these test methods are validated. And then we don't know what the transmission limit we need to look at.

So based on this it is not clear that these methods can be applied to the investigation of potential cross-contamination by MUNJI devices.

Thank you.

CHAIRMAN EDMISTON: Thank you very much.

MR. LIPMAN: All right. That brings us to our panel questions.

The first is identify the scientific questions that need to be addressed to demonstrate whether MUNJI devices are safe for multiple patient use in the United States.

Second, discuss the adequacy and feasibility of the currently available methods to assess the potential for cross-contamination and the risk of disease transmission by MUNJI devices.

The third, Feinman, et.al. in 1984 suggested that a volume of blood as small as 10 picoliters can transmit hepatitis B virus in chimpanzees. However, this finding is based on a single animal study. Considering the potential public health benefit of MUNJIs is there a threshold volume of blood contamination that presents an acceptable risk? If so, what threshold would be considered acceptable?
CHAIRMAN EDMISTON: These questions will be part of the Panel deliberation this afternoon, and they will be repeated again.

Before I go any further, I'd like to ask for clarification from Dr. Lin. In our discussion as we go through this this afternoon are we addressing those pre-amendment devices that are currently in circulation or are we considering answers to questions that will be incorporated into future guidance documentation?

DR. LIN: I think that the answer is both. As you know, the pre-amendment device legally it is still considered legally marketable. Every presenter also mentioned that we also has clear some of those MUNJI device after 1972. So when in your discussion you have to consider all those potential -- all those legally mandated device. So that discussion will be built into our guidance document in this area.

CHAIRMAN EDMISTON: At this time I'd like to invite the members of the Panel to address any questions that they might have to the presenters from the FDA. Yes, Dr. Word?

DR. WORD: I have a few questions. One, if you're looking for new indications or seeking new, I guess, MUNJIs, or that they're all referred to that; are you looking to utilize them in one segment of the population or the entire population?

I guess my question because I come from a pediatric background. Are you saying do you want it for everyone or do you want it just for adults?
MR. WATSON: Actually, I think the answer would be any suggestions you would have in that are would be helpful. Right now they're generally used. There's no restriction on pediatric or adult. The assumption is any appropriate patient that can be used for that vaccine this device can be used on that patient.

So if you have suggestions about that, maybe you think there's a population that is best suited for this, we'd be grateful if you'd offer that suggestion. But to answer your question, right now they're generally used. There's no restriction whatsoever on who these devices can be used for.

DR. WORD: I guess the next question I had was when you looked at safety with your chimpanzee data, you talked about I think it was 10 picoliters were considered acceptable? Anything below that would be acceptable. But yet you stated also that it was known to transmit hepatitis B even if you went below that. And so I didn't quite understand how that number 10 came about. And the reason I say that because if you're looking at using it in a population, we've had universal hepatitis B immunizations for the last 13 years. So we have all children up to 13 and we've had catch-up, and we don't have others. And as one of the public speakers, we don't have hepatitis C that's routinely done.

And I guess my question, and I don't really know what the obstetricians do, I don't know if they routinely screen for hepatitis C. I know they do hepatitis B, and they may not do hepatitis C routinely. I don't think they do.
And if that's the case, then that may not even answer the question if you're talking about using MUNJIs. You might talk about hepatitis B, but still doesn't address hepatitis C.

MR. WATSON: Right. I think I might defer that question to Dr. Bezabeh.

My understanding of it is hepatitis B is the most virulent of the strains and that's why we were looking at hepatitis B. But I'll leave that up to Dr. Bezabeh.

DR. BEZABEH: Yes. What Tony said was right, you know. People have looked at hepatitis B virus because it was the most high infectious and it's easy to measure.

The 10 picoliters was from one study in 1984 trying to measure the minimum amount of blood that can transmit infectious particles. And serial dilutions, they have it right at 10 picoliters. But to our knowledge there's no safe limit, accepted safe limit that would be safely transmit between injection devices. And that's why one of our questions is because what is an acceptable safe limit of blood?

CHAIRMAN EDMISTON: Are there any other questions from the Panel members? Ms. Petersen? Mr. Layton?

DR. LAYTON: Yes, I have a couple of questions. The first is relative to the intended use of the device. Are there separate -- are any of these devices, or are there separate indications depending on the use with respect to intradermal, intramuscular or subcutaneous or can the same device be used for all injections?
MR. LIPMAN: We do usually have different testing for those different indications. Basically, that would be based on the depth of penetration and the ability to get to the desired tissue that the injector is indicated for.

DR. LAYTON: So there are different standards from that perspective?
MR. LIPMAN: Right.
DR. LAYTON: Thank you.

The second question goes back to the 2004 WHO International Conference. Did they recommend a particular test method? I missed that if that was -- they did not? They recommended studies, but not a particular test method.

Thank you.
CHAIRMAN EDMISTON: Dr. Arduino?
DR. ARDUINO: Mine go along with whether it's intradermal or subcutaneous, whatever, intramuscular. For each jet injector are there different settings that you could set or are they separate devices?

MR. LIPMAN: We've actually reviewed devices that have -- I mean, there are a variety of means to deliver at different depths. I'm familiar with different size orifi, orifices, whatever the word is. Different injection techniques potentially -- I don't particularly know how accurate the method is, but pinching the skin to actually attempt to create more tissue to inject into versus, you know, letting the injector just inject directly into the skin
to reach, say, an intramuscular injection versus a subcutaneous injection.

Does that kind of --

DR. ARDUINO: Yes.

CHAIRMAN EDMISTON: Dr. Word?

DR. WORD: Just a question related to, say, let's say if these MUNJIs were available, one of the things when you looked at the adverse effects, because when you came up with the swine flu, one of the things that crossed my mind immediately is that I don't know what my mother received, but I know she told me she thought her arm fell off when she got her flu vaccine in '76. And I don't know if they used one of those. But if you're dealing with adverse effects and if you're saying you're looking at who is administering them, because you're going to have some of that variability. So I'm wondering I don't know how you control for that.

I mean, I can control for it, but easier with an injection. And with the other, I'm just not sure how do you control for that or have you thought about how you control? Or when you talked about contamination, how often do you check to see if there's blood in there?

MR. LIPMAN: The users of these devices would definitely ensure that at least by visual examination that there is no blood remaining on the tip of the injector. But I mean there's the potential for it to get back into the fluid path. You can't always visually identify that there's any presence of contamination present. And that's kind of the issue.
CHAIRMAN EDMISTON: Dr. David, do you have any questions?

MR. DAVID: Yes. I have three questions. One relating to previously asked on the intended use, and mostly on the definition that you give the MUNJIs. And my question would be why not look at some of the cross-contamination principles and look at the device definition by the way of possible contact with the skins exist. For example, devices that might have continuous jet flow, devices that might have various distance gap producing mechanism, etcetera, etcetera. And that would allow, perhaps, some better design of devices and validation of their performance because you're preventing cross-contamination to begin with.

So that's one question.

MR. LIPMAN: We actually have representatives here from a company who is having to design based on those ideas exactly. Felton International is present here, and they will probably talk a little more in detail about the testing they've done on their jet injector. But, I mean, they do actually create a gap. They have disposal skin contacting device you have to inject through certain layers to actually get to the body; the idea being that it would be much more difficult for any of the stream or blood to get back up through that small orifice that's created by the jet and into the fluid path.

So they have attempted to minimize it, but the question still remains how can we
evaluate whether or not they have mitigated that risk sufficiently.

MR. DAVID: My second question relating to your conclusion about the single MDR report that cross-contamination was result of improper use. And since we are reviewing what is considered proper use, I wonder had you reached that conclusion?

MR. LIPMAN: It actually wasn't even a MUNJI device. It was a device that had -- actually it may have been a MUNJI device. But either way, it was supposed to be used for one person only and then either sterilized or replace the fluid contacting components. But instead, the device was actually used for five patient consecutively, and that wasn't the way it was supposed to have been done.

MR. DAVID: I will go back to my first question that I'm not sure that the definition of low load and high users is appropriate.

MR. WATSON: I'm sorry. We have some more information on that last comment.

DR. BEZABEH: Just to clarify the MDR report. It did not document any closed contamination. There was just misuse. So there was no documented transmission or infectional cross-contamination.

MR. DAVID: My third question is about the effort that FDA put into looking historically since it was noted here that the DoD has significant amount of data use of MUNJIs, what are the effort the FDA puts to review that source of data use of MUNJIs?
MR. WATSON: We primarily looked at what was out there in the literature that the DoD had published. We haven't actually received anything directly from DoD regarding safety information about MUNJIs. Most of -- well, whatever the DoD wants people to know is out there in the published literature. Whatever other information is available, may or may not be available to FDA directly. So we've primarily looked at what's in the public domain.

CHAIRMAN EDMISTON: Any other questions from the Panel members? Dr. Lin?

DR. LIN: If I may, just to add to FDA's comment. I think probably for the Panel members probably need to be recognized that this is a 510(k) device. It's close to 510(k) device and I think that the previous presenter has mentioned that we are talking about substantial equivalence; that means that you'll compare the new device with the current market device. You can even compare with a pre-amendment that earlier, like in 1950 something, those device. That's, as I mentioned before, is still considered legally marketed device.

So now when we compare so called substantial equivalence, that means that the manufacturer would have to establish that they are as safe, as effective as those legally market device we call predicate device.

So that's the concept how we so call create this device for marketing. And now that the question is what is considered the criteria to establish a safe as effective, that's the
issue. That's what we try to address. Because the science changed when we review, like early in the '80s or '90s as compared to now. The emphasis is quite different, particularly for in person disease prevention control, quite different. So that when you discuss the FDA's question, please keep that in mind.

And then second comment I wanted to help with that, I think Dr. Word, you mentioned about the use and how FDA treats the users participating. That's most of the time when we do reviewing, we will look at the user's instruction or labeling. And that is also the area we would like to hear your input, too. When we create a guidance document, what kind of information we need to ask manufacturers to clearly indicate in their labeling that we would appreciate your input in that regard.

Thank you.

CHAIRMAN EDMISTON: Now your statement about equivalence really relates to the delivery of an effective vaccine dose or whatever you're delivering. It's not addressing the concept of infectivity or safety from that perspective, correct? But as the last surviving member of that 1999 Panel, it looks like we have a lot more data available to us for consideration than we had six years ago. And the question that I rally have is, you know Mr. Hooks' presentation was compelling. However, it was anecdotal to the point that we don't have any real evidence relative to risk.

And I suspect my question is with the devices that are currently in place, as any
assessment been made in terms of the relative risk associated with the use of these devices in acquiring an infective dose of whether it's hepatitis C, hepatitis B or HIV?

MR. WATSON: Shewit, what do you think about this question? Is this a question that you might be able to answer?

I just want to make sure I understand your question. Are you asking about the effectiveness of actually delivering --

CHAIRMAN EDMISTON: No, not at all.

MR. WATSON: Okay.

CHAIRMAN EDMISTON: What we're talking about now, because I think that's the issue that we have to separate here. We're not really concerned about to a great degree the effectiveness of delivering an appropriate dose of the vaccine. What we're concerned with is how effective is the device at preventing the transmission cross-contamination of an infectious entity.

So my question is relative to '99 when the committee requested a some postmarket surveillance be done, has any consideration been given with the devices currently in place what is the relative risk of acquiring an infectious agent with the current device in place without realizing that to a great degree the risk is associated with the compliance and how the device is being used? So has any consideration been made of what this relative risk might be?

MR. WATSON: I think Dr. Michaud might have an answer for us here on that one?
DR. MICHAUD: Ginette Michaud, Deputy Division Director of DAGID.

I think it's very hard to answer your question. The reason we're here today is to get advice from and recommendations from the panelists as to how we should best assess the risk of cross-contamination due to MUNJI devices, or that potential risk. And so it's very hard not knowing the answer to that how would we determine the relative risk as compared to the earlier designs of these devices.

CHAIRMAN EDMISTON: I appreciate that comment. And this goes back to my first question to Dr. Lin. So therefore our deliberation will have a profound effect on devices currently in place?

DR. LIN: Right.

CHAIRMAN EDMISTON: All right.

Yes, Dr. Word?

DR. WORD: Perhaps you stated this and maybe I don't recall. How many devices are actually being utilized? Because when I looked at it, you said that there were a number of -- you know, CDC recommended it only for risk, you weigh the risk and benefits. WHO doesn't utilize it. And I'm not really concerned about their use, because it doesn't effect the United States right now. I know the impact that we have will eventually have a global effect, whatever recommendations comes from here.

How many devices are actually being utilized?
MR. LIPMAN: I can't speak precisely to the number of devices that are being marketed. I can tell you what I'm familiar with.

We have cleared two dental devices for delivering anesthetic during dental procedures that are MUNJIs. We have at least four cleared MUNJIs for mass immunization intended use. Of those four, there are most likely two that are -- since there are actually, you know, these WHO and CDC policies against using these devices, the manufacturers have, obviously, had a very difficult time marketing their devices within the United States and the world. So I think Felton actually may be able to give you a better idea for how many devices are actually being used and whether they've been able to market their device.

MR. WATSON: One thing to keep in mind is that even though these products may not be widely used anymore, we're still getting submissions for them. And to the extent that we have to evaluate them, we would like some input on what you think we should be doing here. Because we're still a clearinghouse for the world, the FDA. So even though they may not be necessarily marketed here, companies will come to the FDA to get clearance because the idea is get clearance and FDA and a lot of the rest of the world will accept that. And we would like to be certain that whatever we're clearing is something that we consider clinically acceptable here, not just based on previous standards for clearing these products.
So the actual number, we don't really know that. We don't really have records for that here. But we do know we get asked to clear them. So that's sort of one of our concerns.

CHAIRMAN EDMISTON: Dr. Butcher, do you have a question?

DR. BUTCHER: It's been answered.

CHAIRMAN EDMISTON: Are there any further questions by any members of the Committee?

I think we'll move on to our next presentation from Dr. Martin Friede from the World Health Organization.

DR. FRIEDE: Well, thank you very much for inviting me to attend this. And I would like to reiterate something that was said a few moments ago. The recommendations from this Panel will have a global effect.

So, first, I'd like to apologize. I have modified my slides slightly compared to what you received. And this is because I learned last night that Dr. Weniger was not able to attend. So I have added some more background slides. So I hope this does not effect what you have too much, but there is some more data.

So if we'd please go into the first slide.

So we've already heard quite a lot of background about the early history of safety concerns. And, unfortunately, my eyes are getting worse and worse with age. I can hardly read that myself. But let's go through this.

If we begin around about 1959 there was already an evaluation done using precipitin
test for human serum. And this really showed up negative. And this group in 1959 were also unable to transfer hog cholera from one viremic pig to another. So this was really the beginning of the evaluation of safety.

In 1962, though, Eli Lilly & Company, I'll show you this in a moment, but on their inference of product insert, that bleeding could occur and that this would carry a risk of hepatitis, and that it recommended to the doctor that if blood was observed, then resterilization should be done.

1970 bleeding was noted on the nozzles, on the skin and blood on the nozzles. And it was hypothesized that disease transmission could occur.

And in another 1970 paper there was an increased detection of albumin on nozzles.

And 1981 there was a study done, this time negative, no hepatitis B surface antigen detected by radioimmunoassay after injection of just two volunteers, both of whom were hepatitis B carrier patients.

Next slide, please.

So I certainly can't read this, but I know what's written there. This is the product insert from the 1962 package from Eli Lilly and it states somewhere there under red lined that if bleeding does occur, and bleeding does occur sometimes with jet injection, then the nozzle should be resterilized. So there was recognition then that hepatitis B transmission could take place.

Next slide, please.
Well, I think the change to the world jet injection took place in 1985. And in 1985 suddenly we had evidence of risk. This was the very well known case of the weight loss clinic in California where a hepatitis B outbreak took place. But I would like to emphasize, this is a fairly unique situation. These were people coming back time after time. I believe it was 15 to 30 times over a two months period. Back to the same clinic where they were being injected in the same small population where there must have been one high titer carrier that was there who could reinfect this population. Also, one this one single device and was this device being properly used. So this opens up a lot of questions of how to ensure that devices that may appear to be safe, how do we ensure that they are being properly used and how do we ensure that they are retaining their safety over time and in the hands of everybody?

Next slide, please.

This is some data taken from that California study. Printed in the Morbidity Weekly Report. And this shows that when the jet injector was no longer being used in that clinic, we began to see a decline over the next several weeks of hepatitis B onset. So this was really the proof. But we must recognize that this is not quite the same situation as immunization where you typically go and get one injection, maybe once per year.

Next slide, please.

So after 1985 the world changed slightly, and suddenly people really began to
look at what were the risks of using these. And, again, I'm stretching my eyes to see this.

1985 there was a demonstration done that the LDH virus, this is a mouse lactic dehydrogenase virus, could be transmitted experimentally between mice using a jet injector. Again, a comment here. How does the thickness of the skin of a mouse represent a model for human beings? And if you were to give a mouse a jet injection with an injected aim to give intramuscular injections, this would probably cause a tremendous damage to the mouse.

1980[1988 sic] hepatitis B was found on the skin on the site of injection, however it was not found on the nozzles of the injection.

1994 this was a study by Mr. Brito. Blood detection in the ejectates. So the volunteers were injected and then the next shot was put into a tube. And they were using the forensic occult blood detection stripes which measure about 2,000 picoliters as limit of detection. And in roughly one percent of the ejectates, blood was detected.

Now this introduces the concept of picoliters. We've already heard brought up this concept 10 picoliters is the minimum level of blood that can transmit infection. I hope that in my presentation I will show you that this is not a scientifically sound observation, but we will see how we can address this.

So already at 2,000 picoliters, one percent of the ejectates did have blood in them.

1997 a VEE virus was transmitted between animals using three Russian jet
injectors, one of which I understand is the originator of the Felton device which has subsequently been prior approved.

1997 a very interesting paper published from Bulgaria, Dimache, et.al., this was in *Vaccine*. Now this is interesting because no hepatitis B transmission was observed in population. So this is a field study. 38,000 intradermal injections were given with a disposable spacer, which they claim was something like a protection cap. And this is very interesting. We'll discuss this in a moment as to what this does not mean.

2001, this has already been mentioned, a meta analysis of hepatitis B in Brazil showed that people who had received the yellow fever vaccine via a jet injector were much more likely to have also been infected by hepatitis B.

Then two studies that I will briefly discuss have already been discussed. 2001 the calf model, serum albumin was detected in the ejectates, and that's an unpublished data already discussed about a clinical model.

Next slide, please.

So in the calf model what was done here is that four different injectors were used and saline was injected into the calves and then injected into a tube. And using a calf or a bovine serum albumin assay looking to see what was taking place. What is important out of this is that you see that there are a lot of samples that have between 10 and 50 picoliters and quite a lot that have between 50 and 1,000 picoliters.
of serum albumin. So this shows that all four of the old model jet injectors were transmitting quite often quite a significant amount of blood. Certainly what we would consider to be an infectious level of blood.

Next slide, please.

Now this is unpublished data. Again, coming from Brazil using, again, old model injectors. And when I refer to "old model injectors," I am comparing this against improved injectors that may be available soon.

What was done here saline was injected into the volunteers and then three injections were made sequentially into a tube. And using a human serum albumin study looked at how much blood was there. Now this study had, apparently, a limit of detection of 10 picoliters. So wherever you see something positive, it simply means greater than 10 picoliters.

And what we're seeing here is whether it was wiping with the nozzle or wiping without the nozzle, we had between 7 and 11 percent of the ejectates were contaminated with blood. However, what was also done in this study was injecting saline into the tubes before injecting people. And you see there are positives there. So this really begins to question this assay. We were getting false positives here. And I will discuss this later. But the reliability of this assay is doubtful.

Next slide, please.

So what has been the reaction of the public health organizations? First of all,
we've had over 2 billion immunizations given worldwide from 1952 to 1990. We've had warnings on the risk of blood transmission. We've had the hepatitis B outbreak. So in 1987 WHO recommended restricted use of these devices. And finally in 1996 we actually recommended against the use of these devices.

And from 2000 to now there has been the development of new generation devices aimed at overcoming these safety concerns.

Next slide, please.

So I'd like to summarize and the rest of the meeting summarizing a meeting that we had in March 2004 which was aimed specifically at determining the safety of these new generation devices. And by "new generation devices" I mean devices that are aimed at overcoming these safety concerns; that have a built in safety device.

The questions are how infectious is blood? How do we measure it? How do you model the risk? What level of risk is acceptable? And our conclusions.

Next slide, please.

So this is, I think, possibly my most important slide, is how infectious can blood be? We've already heard that hepatitis B is far more infectious than hepatitis C, which is more infectious than HIV. And there is a CDC reference for this. Now we've heard the statement that 10 picoliters is able to transmit infection to a chimp. This comes from the Bond, et.al. paper 1984. Ten picoliters could infect one picoliter could not. However, this was one
study on one sample. So it means for that sample of serum had that type of viremia, 10 picoliters was able to, one picoliter was not. And that's all that means.

So at the meeting last year we tried to answer the question of how infected is hepatitis B. And you see over on the right hand side a graph which is taken from the Lindh paper. And this shows two lines. The upper line are people who are HBE positive with the HBE antigen. And it shows their viremia in terms of genome equivalence per milliliter. The average is around about 10 to the 9. It goes up to 10 to the 11. However, we also heard at the meeting last year that in rare cases when people have both HIV and hepatitis B, viremia can go up far, far higher; 10 to the 12, 10 to the 15 even.

So for the rest of this discussion I have just assumed that 10 to the 9 is an average amongst these HBE positive carriers. And we have done a bit of modeling and assumed that hepatitis B carriers, of these 20 percent have high viremia, and this 10 to the 9.

And the conclusion of this is that a fraction of a picoliter can transmit infection. So if you have a viremia of 10 to the 9, this means you have one genome equivalent per picoliter. But there's a probability, of course, that you may have more than one genome equivalent per picoliter because you never know how these things are being distributed. And also you may run into somebody who has a viremia of 10 to the 15, in which case one picoliter may have a very high number of genome equivalence.
So the next slide, please.

Because of the recognition that we have to go below 10 picoliters, we were looking at assays to measure blood contamination. Now the human serum albumin assay had been developed as a surrogate marker. Since human serum albumin is the main protein component within blood, it was felt that this was a good target to be going for to measure how much blood could be on the nozzle. This was developed by Kings College in London.

And an improved assay was developed by them where they claimed they could develop, approximately they could detect approximately three picoliters. That was limited quantification, limited detection, about one picoliter. However, as has been already mentioned, serum albumin is everywhere. It's in our spittle, it's on our skin, it's in our hair. And for example, dead skin may not have any probability of transmitting infection, but it will give you a positive single. So this presents a lot of problem using the human serum albumin assay as a surrogate marker for blood.

Also, when WHO sent this assay out to two independent laboratories, we discovered that you could not validate this assay and it was the independent laboratories gave limited protection or limited quantification between 15 and 30 picoliters. So it was therefore a requirement for a more reliable and more sensitive assay.

Ideally, we need to be able to really measure infectivity. Measuring blood volume, per se, doesn't tell you much. So we felt that a PCR
analysis of, for example, the hepatitis B virus from highly viremic carriers, this gives you an idea of really how much, what's the probability of getting infected.

Next slide, please.

Here this shows the comparisons. When the Eli Lilly product insert said if you see visible blood, resterilize it, that's about 0.1 microliters. There's a limit of what you can see. Chemical blood tests is about .01 microliters. Measuring surface antigen with an analyte is about .001 microliters. The albumin assay, 15 to 30 picoliters. And we believe that using modern techniques you can detect hepatitis B virus at about 3 genome equivalents. So this would be about 3 picoliters of that high titer serum.

So we then tried to -- since we accept that you can get disease, you can get disease transmission with less than 10 picoliters, the question is how do you model this risk? We have to have an idea of what risk is there with one picoliter. What risk is there with .1 picoliters? And this begins off with the assumption that risk of getting hepatitis B virus is proportionate to the endemicity. It's logical. If you are in a room where 50 percent of the people in the room are hepatitis B carriers and you will be receiving a jet injection subsequent to one of them, you have a higher probability than if you're in a room where there is only 1 per 1,000 with this. So that's logical.
In the USA you have less than 2 percent carriers. This is WHO figures. In Africa, Sub-Sierra in Africa, there are between 8 to 20 percent of the population that are hepatitis B carriers.

So let's go into some very rough modeling. This was presented at the meeting last year. And I've just tried to summarize this taking one or two examples. If, this is a very big if, if each injection transmitted \(0.5\) picoliters, now this would be safe by our PCR assay that I just discussed which is measuring about \(3\) genome equivalents. So \(0.5\) picoliters would pick up nothing. We would say safe.

If 2 percent of the population were carriers and if 20 percent of these were HBE antigen positive, in other words high titer carriers, then also if one ID50 was \(10\) genome equivalence -- I should mentioned that WHO tried to find out from hepatitis B experts what is the ID50. How many genome equivalents does it take to transmit infection?

We heard from Bob Purcell, not at the meeting. This was by oral communication he gave us. That \(10\) genome equivalence may do it. We heard other experts said maybe a \(100\) genome equivalence do it. So we don't really know. But we're taking a worse case scenario and say \(10\) genome equivalence could transmit infection.

Now, we can do some mathematics on this. And this would say that on a population with \(10\) to the \(9\) genome equivalence per millimeter, which is your high titer carrier, one ID50 would be \(10\) picoliters. But what happens
if you are giving less than 10 picoliters? So we worked out a mathematical formula which tries to express the fact that this is not a linear decrease, but we expressed the probability that N ID50s give you an infection as being one minus, not 25 to the N.

You could also get roughly the same number by just dividing the number of microliters or picoliters that are being given by the 10 picoliter sample, which contains your ID50.

In this case the probability of infection on receiving .5 picoliters from a higher viremic carrier is .034. And then to calculate the probability of infection, you have to work out what is your probability of this person being in line in front of you, which is the probability of having your hepatitis B carrier there and the probability that that hepatitis B carrier is a highly viremic carrier times by the probability of the .5 picoliters carrying an infectious dose. And this comes to -- you've got the numbers written there. .000132, which means that they could be up to -- and I emphasize up to 132 infections taking place per million injections.

However -- next slide, please -- I'd like to really show the caveats of this. First of all, the ID50 that I took there was 10 genome equivalents. This is the most infectious that we've heard from. Other scientists have said it's more like a 100. So this would bring us down to 12 infections per million.
Now, first of all, the studies that have been done including the Bond study in 1984, the serum was injected intravenously. Now when we give jet injectors, this is not intravenously. So it could be that by giving nonintravenous delivery, we are also going to decrease the infectivity by not getting to the blood, not getting to the liver. So this could drop this down even further.

Also, there may be other factors such as drying. The numbers that we get there, this is the worst, worst, worst situation, the worst case scenario possible. It assumes a linear risk. It could very well be that below a certain viral load the risk may be infinitesimally small. And it also assumes that every ejectate is contaminated. So that is the caveat for this and it gives us a number.

Now let's look at risk assessment in field trials. I already discussed briefly this Dimache study 1997. This was a slightly new generation injector. It had a disposable spacer. It was not really a protector cap. 38,000 injections were given in adults. This was in Bulgaria where the hepatitis B endemicity is 5 percent. And these volunteers were followed up for six months to determine how many cases of hepatitis B virus infectivity took place subsequent to the immunization, which could be ascribed to cross contamination. And absolutely none took place. No observed hepatitis B infection in vaccinees. However, this was a low volume injector. It was delivering .1 to .2 mls intradermally. This is not the same as the
studies we talked about previously which were typically intramuscular or subcutaneous with 0.5 ml. Intradermally one could imagine a lower splash back.

Zero out of 38,000 observed infections. The upper 95 percent interval of this is 4 per 38,000. So we could be having a risk of really 1 per 10,000, risk of infection and still observe zero to 38,000 in a field trial.

So the field trials to prove safety would require very careful design to give power. And I think this is one of the real difficult questions here. When we're dealing with such low figures of shall we say 10 per million or a 100 per million infectivity as being the possible risk of a device, how do you see this signal above the background noise?

If you go to Sub-Sierra in Africa where you have a background and a high rate of infectivity taking place, you have a high noise. So how would you see your relatively big signal. If you do this in the USA where you have a relatively low background, you will also have a very relatively low signal.

Determining your signal to noise ration in a field evaluation is going to be exceptionally difficult.

Next slide, please.

So the conclusions of the WHO meeting were that sub picoliter levels of blood can transmit disease. Ten picoliters is not a scientifically valid number.
Available blood markers, which were the serum albumin, are inadequate as surrogate markers of safety. However, PCR detection of hepatitis B from highly viremic carriers is much better.

It is feasible to evaluate safety for a small sample size by PCR. However, how does one take into account device aging and device misfunction? And I'd like to bring up a question here for your consideration, which is how do you determine the reliability of the safety mechanism? You may prove that your device is safe in a small trial of a 100 people, but how do you determine that the device is reliable over a long term? This would probably require ex vivo and in vitro studies, but this will have to be considered.

We also concluded that it would be very complex to evaluate safety for a large sample size. So, first of all, going from this small field study using highly viremic carriers to the population which you're actually using the device in the population, we could not determine the ethical pathway to get there.

Next slide, please.

So, WHO position. The determination of the safety of MUNJIs is the responsibility of national regulatory agencies. WHO will not determine the safety. This is the responsibility of the national regulatory agencies.

Secondly, if used properly needle injection is safe. Now this is a big if. We know that the injections are not always done properly
and we know that disposal is not always done properly. However, if done properly it is safe.

To the WHO is not acceptable to replace injection by a technology for which the safety is questionable. So while we have questions on the safety, it is not acceptable to replace needle and syringe.

Needle-free vaccine delivery is desirable. We recognize this. If we can get rid of needles from the immunization program, this would be fantastic. Given for the moment the questions on the safety of MUNJIs, we believe that disposable cartridge injectors where there is no reusable path or appropriately safe alternatives, whether or not they're cost effective is another issue. We are evaluating the use of these for vaccine delivery.

Now, I'd like to finish. Next slide, please. With two slides. First of all, these are the points for consideration.

We've already heard about the advantages: There's no sharps, there's no waste, it's fast and it is low cost, very low cost per injection. The comment to this is that there may be a risk. Whether the risk is a real risk, whether it is a risk that is perceived by the population, this could really be inhibitory of these devices.

Daily cleaning and sterilization of the fluid part is required and there may be a risk if this is not properly performed. We know that ensuring the use of syringes properly is difficult ensuring safe cleaning of these
multiuse devices may be complex. And we also face the problem of the cost per device.

Under what circumstances is high speed injection required? It's required really where you have a low ratio of health care worker to population or where you have centralized, not dispersed health care.

And finally, what level of risk is acceptable? So I think we really have to balance the risk benefit here. Needles injection is not always performed safely. Needle stick injuries do occur. Needle disposal is not always performed safely. However, for the individual, an individual receiving an injection from a sterile needle and syringe runs no risk. So we have to look at the risk to the individual compared to the risk to the population, and I think that is a question for the Panel.

Thank you very much.

CHAIRMAN EDMISTON: Thank you very much for traveling to Washington and making this presentation.

At this time this presentation is open for any consideration. Do any members of the Panel have any questions for Dr. Friede? Yes, Dr. David?

MR. DAVID: I have two questions. One is relating to the comment you made about the disposal cartridge. What do the study looked at when they looked at this puzzle card as far as volumes and so on?

DR. FRIEDE: There has not yet been a study. We are beginning to evaluate these.
MR. DAVID: So your statement about it is an alternative safe is based on?

DR. FRIEDE: It's simply because there is no reuse of the fluid part, there is no reuse of the nozzle. There cannot be transmission of blood from a nozzle because the nozzle is not reused.

The definition of a MUNJI was given previously, earlier on this morning, as being one where the fluid part is reused. In the disposal cartridge the entire fluid path, the entire -- the whole fluid path, the whole nozzle is used once and cannot be reused.

MR. DAVID: I see. So the whole fluid path is replaceable then, that's the point?

DR. FRIEDE: Completely.

MR. DAVID: Okay. And if we can go back to your risk model slide. Where was it.

DR. FRIEDE: Next one. That's right.

MR. DAVID: Can you just take me again through the ID50 argument.

DR. FRIEDE: Okay. The one figure that we received from Bob Purcell suggested 10 genome equivalents is an ID50. So let's just take that as a starting point. Other people have said 100.

Now, if you have 10 to the 9 genome equivalence per milliliter, this means you have one ID50 in 10 picoliters. In other words, if you receive 10 picoliters, you have a 50 percent probability of becoming infected by definition of the ID50.

So the question is if you receive less than ten picoliters, if you receive one
picoliter, what is the probability in one picoliter that you are going to have ten genome equivalents? So this is our applying the statistical laws.

You have a random distribution of your ten genome equivalents per -- I'm sorry, your 10 to 9 per milliliter. What is the probability that 10 genome equivalents are going to be found in one picoliter?

MR. DAVID: Okay.

DR. FRIEDE: The way to do this is to use that formula. Okay. This is an expediential formula. So the probability that you will find an ID50 in one picoliter is going to be 1 minus now .5 to -- it's going to be one divided by 10.

MR. DAVID: So you're making actually two arguments. One is the volume of the injected and the other one is the site intramuscular or intravascular as two mechanisms?

DR. FRIEDE: The caveat is this concept of 10 genome equivalents, this comes really from intravenous studies. And it could very well be. I'm putting this as a caveat, as a scientist, that when we deliver this intramuscular and it doesn't get straight into the capillaries or into intravenous system and go to the liver, it might take a far number of genome equivalents. This is a worst case scenario if you take all available data that we have. So we're really looking at what the worst number could be.

MR. DAVID: Okay.

DR. FRIEDE: And with that number, you see that your signal is quite small and it
really opens up the question of how would you see this in a population.

DR. ARDUINO: But when we get to risk, because I'm doing some stuff with biodefense stuff, an ID50 may not be acceptable. What happens when if you shift the curve and want to look at an ID10 or an ID1? Well, your number gets how many -- you know, it gets a lot smaller, doesn't it?

DR. FRIEDE: It does. I put this really as a method of looking at it. Now those numbers there are not validated numbers. These were numbers that we put up as a method of approaching this to enable you to accept the fact that 10 picoliters is not a number, is not suddenly that below 10 picoliters nothing happens. Things can happen below 10 picoliters. We need to determine what is the worst probability that something will happen?

CHAIRMAN EDMISTON: Any other questions from the Panel members? Dr. Layton?

DR. LAYTON: Yes. I have a question on the risk assessment, the Rumanian study where you talked about the lower splash back risk than 0.5 ml intramuscular and you had a question mark. Would you care to elaborate on that relative to this intradermal versus intramuscular and any of your observations or knowledge relative to the knowledge relative to the level or degree of splash back?

DR. FRIEDE: That I put up -- we have it on the slide.

This is, as a scientists, I just imagined that if you inject .1 ml intradermally,
you're going to have a much lower risk of forcing body fluids back up onto the nozzle than if you inject a larger volume deeper. Intradermal probably shouldn't really be giving you any blood, and there's not much going in. The volume coming back is probably going to be a function of the volume going in, and also the elasticity of the tissue that it's going into.

So I think looking at this study it's an interesting study, but as I said there are two caveats here. One is it's intradermal and low volume. And what I really wanted to bring this up for is that seeing zero in this population doesn't tell you a lot.

DR. LAYTON: Thank you.
CHAIRMAN EDMISTON: Any other questions?

I have a question. From your perspective what troubles you about these devices? Is it their design or the hydraulics? Because obviously these devices are not going to go away, especially in a circumstance where we need mass immunizations.

DR. FRIEDE: Okay. There's two things that worry us. And I give you the official point of view here.

The first one actually is to do with the maintenance of these. That in the populations which are our responsibility to reintroduce a cleaning procedure which has to be done, and the maintenance, this is a very big problem for us.

The second problem is that while there is concern of safety, any concern, for us
to impose on countries to use this device just carries an enormous risk that until we get really clear evidence or a clear consensus that this is safe, it is going to be difficult for us to recommend to countries to use this. Because any incident that took place would come back and we would struggle to say we confident that that incident, your infection, did not occur because of the device. So until then we are standing by our policy, which is that immunizations will be given with auto-disabled syringes. And that the auto-disabled syringes will be provided with sharps disposal boxes to try to ensure that sharps disposal is done correctly.

CHAIRMAN EDMISTON: If the devices are used in a compliant manner the way they're meant to be used, do you think the devices are safe?

DR. FRIEDE: The devices that we have seen without a protection cap, we have data from the calves and the data from the Hoffman study in Brazil to show that frequent contamination of the ejected did take place. And that contamination was clearly of a level of blood that we are convinced can carry disease. So the devices which do not have a protection cap which are to be used for giving intramuscular injection we are convinced that these carry a significant risk.

CHAIRMAN EDMISTON: Okay. Any other questions by members of the Panel?

Well, thank you very much for your time.
I've been informed that we can do lunch. Actually, we're about half an hour ahead, which is terrific.

I'd like to invite you all to lunch, and we'll meet back in one hour.

Is industry going to be making their presentation? Is 12:00 fine for industry presentation? Is everybody here. Okay. Well the plan at this time is to reconvene at 12:00 and begin our industry presentations.

Thank you.

(Whereupon, at 10:58 a.m. the meeting was adjourned, to reconvene this same day at 12:00 p.m.)

A-F-T-E-R-N-O-O-N  S-E-S-S-I-O-N  

12:05 p.m.

CHAIRMAN EDMISTON: I would like to now call the meeting back to order.

I'd like to remind the public observers in the audience that while this portion of the meeting is open to observation, public attendees may not participate unless specifically requested to do so by the Chair.

We will now continue with industry's presentation related to today's topic. And we have Mr. Darin Lee Zehrung, did I pronounce your name correctly?

DR. ZEHRUNG: That's correct.

CHAIRMAN EDMISTON: He will be addressing Program for Appropriate Technology and Health.

DR. ZEHRUNG: Thank you.
Do I have to make a conflict of interest statement at this time?

CHAIRMAN EDMISTON: Yes, we would appreciate that.

DR. ZEHRUNG: Well, PATH is a nonprofit organization, nongovernmental. It is focused on improving health in the developing world. And we're actually working with a couple of different needle-free injector developers, one of which is Felton International, and that's the technology that I'll talk about today. It's a collaboration with different developers that includes a development portion as well as clinical testing. But we do not receive any funds from these manufacturers, and actually we're self-funded by different donors.

Next slide, please.

So, as I said, PATH is a nonprofit organization. And this is our mission: To improve the health of people around the world by advancing technologies, strengthening systems and encouraging healthy behaviors.

Actually, I'll hold there.

We've actually been involved in the development of safe injection technologies for the past 20 years, either disabled syringes, Uniject which is a prefilled injection device, sharps disposal technologies all focused on improving immunization safety in the developing world. And I work within a program called Technology Solution within PATH, which is that is our prime mission.

Next slide, please.
So we talked about this earlier today. What's the technology need for a high speed needle-free injector? There's the application for mass immunization campaigns. In the developing world examples are measles, yellow fever, meningitis and there are other examples. There are also emerging vaccines that in the development pipeline that could also be a good application for high speed, high throughput, high numbers of injections for those in the developing world such as meningitc which is focused on West Africa, malaria vaccines and also human papilloma virus vaccines.

Pandemic outbreak is also another key application for this technology. Influenza, you know we've read these recent articles about avian flu and the potential for outbreak.

There's really not a technology that exists that could provide high throughput, mass immunization to those vulnerable populations, either in the developing world or in the United States or Europe, for that matter.

Bioterrorism response is also another important application. And I think that I'd actually like to hear from others that represent perhaps that perspective to see if this technology or what their plans would be to respond to an outbreak or even a bioterrorism attack.

And then there's the military application. Although we heard about earlier issues with devices, the first generation MUNJI devices, so to speak, there could perhaps still
be a need for a high speed injector in the military.

Next slide.

So this is actually a slide that I received from Dr. Bruce Weniger, and unfortunately he could not be here today. He's actually Mr. Needle-Free Injector at CDC. And I think he has a very prominent position in the needle-free injector community. And he's done a lot of work on looking at the efficacy of needle-free injectors in delivering multiple antigens. So this is a list. And I think we saw an earlier version of this in a presentation this morning where there is great historical evidence, over decades of use, needle-free injectors delivering different vaccines. Perhaps with the new combination vaccines and newer vaccines in development there is not this clinical history, but it's clear that needle-free injectors are effective in delivering vaccines.

Next slide.

So this is a technology that we are collaborating with in terms of Felton International. They're the manufacturer. And, actually, if there are more specific questions about the technology, I would defer to my colleague Dr. Anatoly Loskutov from Felton International who could perhaps provide more in depth answers.

I'd like to point out that we see this technology as a design hybrid. It's really not a MUNJI. There is a reusable fluid path,
yes, but there's not direct nozzle to skin contact.

The key feature of this technology is that it utilizes a protector cap as a disposable shield. And actually I've passed around samples of this protector cap to the Committee members. This shield is intended to prevent cross-contamination. And we've been involved in collaborating with Felton over the last several years, a combination of in vitro and in vivo testing to build the safety profile for this technology to demonstrate that it does, indeed, prevent cross-contamination.

The current spec for the device is that it has a fixed half cc dose. It's intended for subcu delivery, which most of the developing country mass immunization campaigns deliver a half cc subcu dose. But with different orifice sizes you could either achieve an intradermal dose or intramuscular. We focused on subcu for the current specs for the technology.

And it's hydraulically powered. It does not require electrical power. It utilizes a foot pedal and hydraulics which compressed a spring within the hand piece. That provides the energy then to provide the injection.

And we've targeted in terms of the spec six injections a minute. Now, it's not as quick as the earlier first generation MUNJI devices, but it's more rapid than needle and syringe delivery. So, therefore, still we would consider it a high workload device.

It also requires steam sterilization of a reusable path. Let me point this out here.
So this is the hand piece here. This is the fluid path portion. So that's detached from the hand piece, cleaned and then steam sterilized.

And actually, I think Jason Lipman mentioned this, there are few technologies, MUNJI devices that have received 510(k) clearance post-amendment era. And this technology is one of them. Well, actually last year in 2004 this particular design received a special 510(k) clearance based upon an earlier 510(k) clearance for a device called the BI-3M, which was originally a Russian design. Dr. Loskutov comes from the original design group, and perhaps he could talk about that for those that are interested.

Next slide.

So unfortunately, I had a video demonstrating the technology. It doesn't work. So what I'd like to offer is for the Committee members that are interested -- okay. Well, for the Committee members, I'd like to offer I could bring my laptop to show you the operation of the technology. And then, again, anyone from the public observing, if you have questions please feel to contact me or Dr. Loskutov and then we'll demonstrate the technology.

But basically the protector cap is placed on the nozzle face. Let me go to the next slide. It incorporates a space between the nozzle and the injection site. The injection stream passes through a thin polyethylene film. And once the injection stream penetrates that film, that enters into the tissue. And any
splash back, any contamination is then contained within the protective cap. And for the next injection, the protector cap is discarded and a new sterile protector cap is placed on the nozzle face.

Another key feature about this protector cap is that it's auto-disabled. Once you eject it from the nozzle face, it's disabled so that if you were to put it back on the injector, you could not provide an injection through that spent protector cap.

One key features and perhaps Anatoly could speak to this that's development now and it will be available for the next design iteration, is an interlock which would require placement of a protector cap on the nozzle face for the device to operate. So perhaps, Jason, you'll see that in a subsequent submission.

So in terms of the benefits of the technology, a key feature: Prevents cross-contamination. It uses a protector cap. And I think that the PATH position is that we believe that this technology can be demonstrated to be safe. We could talk about the safety design, we can talk about sample size, but we have the confidence that this technology could have great application and would be a safe technology eliminating needles from use in mass campaign scenarios.

It's also high speed, as we talked about. It allows for rapid response.

One key feature and one feature benefit that we see is that it protects health care workers. There's no risk to needle stick
injuries. And in a mass campaign when you're dealing with large numbers of individuals, at least in the developing world, we have mountains of sharps waste that you need to discard it. And Dr. Friede had mentioned that the current policy is to bundle safe injection boxes, sharps waste boxes, with those auto-disabled syringes. But there's still the potential for health care worker needle stick or for community needle stick injury in terms of the general public.

Many times these syringes are buried in a pit behind a health care center or there's an attempt to incinerate them or burn them. Many times unsuccessful. So that there is a general need, an acute need, for a needle-free technology.

Next slide.

So, are main focus in this project has been to conduct safety testing of the protector cap injector, the Felton device. This project has been funded by the Bill and Melinda Gates Foundation. He's very interested in this technology for mass immunization.

And there have been a number of in vitro and in vivo studies that we've conducted. What I'm going to present are our recent studies. There are studies that we have conducted over the last several years that I won't discuss today, but if you're interested I could provide that information after the meeting.

So fluorescein testing as a simple model. I think earlier we talked about the challenges of identifying an appropriate animal
model. Our focus has been to focus on a bench test model using a very sensitive assay and marker to demonstrate that there's cross-contamination that does not exist.

And then the focus our human safety testing has been hepatitis B virus detection. You know, from the WHO meeting that was held last year, we took that input and we focused on a method, identifying a method that could be used to detect hepatitis B virus in subsequent injections.

Next slide.

So for the fluorescein safety testing we use a very highly concentrated fluorescein dye, and that's a surrogate for high titer HBV infection. And the detection limit of this current approach is .04 picoliter.

I think that we've talked about picoliters and volumes of infectivity throughout the meeting. And I think that for some it might be a little unclear, but really what it means is that it's about 100 fold more sensitive than available PCR methods.

The original design of this fluorescein test focused on the 10 picoliter threshold. But given the input last year at the WHO meeting, we put that aside and just focused on if anything could be detected with the method, then that would be the definition of contamination. So I think that the current results that I can show you demonstrate that with the protector cap injector there's no cross-contamination in comparison to predicate
devices such as earlier MUNJI devices there is demonstrated cross-contamination.

The samples that are generated in the PATH laboratory are sent to a third party laboratory, MDS Pharma in the base outside of Seattle, Washington. And they use their equipment to analyze samples.

Next slide.

So thanks Dr. Friede, he gave me this slide earlier today. So I would like to stress my appreciation for this.

What I want to point out is that in comparison to the other contamination assays that Dr. Friede had presented, the fluorescein assay really exceeds the PCR methods in terms of a detection limit. So it's very sensitive, it's very specific in terms of an assay. And we believe a good surrogate aside from human testing to demonstrate cross-contamination safety.

Next slide, please.

So you may not be able to see these pictures. This is a first generation MUNJI device. I think that those are familiar with these technologies know what that device would be called. And you can see after injection into the test fixture, there is contamination at the injection site. There's a combination of splash back as well as contact contamination during the injection process. You see that it's contaminated with the fluorescein dye.

The same is true for the protector cap injector. This is the protector cap on the nozzle face itself. It's hard to see in this
photo, but this protector cap post injection into the test fixture is also contaminated. But the down stream sample collected after injection into the test fixture is demonstrated to be free of cross-contamination.

Next slide.

So this is a slide showing the comparison of first generation MUNJI testing with this method versus a protector cap injector. These are the number of samples. So for a 100 samples with the first generation MUNJI device, all were contaminated, a 100 percent with an average contamination rate of 268 picoliters. In comparison with the protector cap injector for 300 samples, all samples were free of cross-contamination.

So the conclusion is that the protector cap prevents fluorescein contamination of the fluid path. And, again, we believe that this is a very useful and powerful method to demonstrate contamination risk with the earlier devices and then lack of that risk with the new generation protector injector.

Next slide.

So for human safety testing, as I said, we've been focusing on detection of hepatitis B virus. And given the recommendations from the WHO Committee from last year, we focused on recruiting high titer individuals that have greater than a million copies per ml and injecting them with buffered saline, and then collecting the next dose and assaying that for presence for Hep B and A.
Currently we're implementing a pilot study in Pasadena, California at the Huntington Medical Research Institute, the Liver Center there. Working with Dr. Myron Tong.

We're focusing on recruiting high titer volunteers, as I said, but also to HBV negative volunteers as controls. And one key feature of this study is that it's a nonsignificant risk study by our definition, that the fluid path is sterilized between use with different volunteers. And so there's no chance of cross-contamination.

We're using an assay that was developed and actually licensed for use in terms of blood screening products in the United States by National Genetics Institute. It's called Ultraqual. And it's also a NAT assay. It's a nucleic acid test. So it's a very sensitive test. And I have results from a validation study that was conducted last year prior to initiating the safety study which was started September of last year to demonstrate the sensitivity and the limited detection for that particular test.

This did receive both PATH IRB as well as Huntington IRB approval. And we're currently continuing to recruit volunteers for this study.

Next slide, please.

So, the study endpoints primarily is to determine if there's HBV contamination in down stream doses. But secondarily, we're also assessing the pain of the injection site and any injection site reaction. So that's also
collected in terms of the study, the information from volunteers.

As I mentioned, there's two sterile saline injections per subject, one in each deltoid. So after injection into the deltoid, the NET is collected. And then that's sent off to NGI for testing.

There's also four negative control samples per volunteer that are being collected. Two injector samples prior to injection into the deltoid that are collected to demonstrate that the injector is free of cross-contamination, but also to determine if there is any background contamination of HBV in the examination room where the injections are taking place. Also two air samples are collected. These are test tubes that are left open in the test tube rack right adjacent to where the injections are taking place in volunteers. Once the injections are completed, then those are stoppered and the whole group of samples are sent to NGI.

Additionally, another blood sample is collected the day of injections to reconfirm titer levels. So for initial enrollment there is a blood test that's conducted to determine titer level, and that's a condition for enrollment into the study. And then the day of injections there's another blood draw to demonstrate that there is still high titer viremia in the particular volunteer.

Next slide.

So in terms of the assay itself, this is used for blood product screening in the United States. And it's also uniquely used by
the Liver Center for HBV titer level determinations. It's part of their clinical diagnoses screening. And HMRI has a close relationship with NGI, and that influenced our decision to work with both HMR as well as NGI.

It was validated for use in the pilot safety study last July.

And the mean sensitivity was determined to be 1.589 internationally in its per ml, which is about 5.4 viral copies.

The 95 percent detection limit is determined to be 6.316 international units, which is equivalent of 21.73 copies. So what it means in terms of a half cc volume, it's about 10 viral copies that is reliably detectable with this method.

Next slide.

So this may be a little hard to see. To date we have recruited five volunteers. I have to say that it's been challenging to identify and recruit and gain consent from volunteers.

You know, we've talked about 10 to the 9th as an average in terms of viral load, but in terms of this Liver Center and the majority if not all the patients are hepatitis B infected, it's very difficult to identify those that are greater than a million copies per ml. We have identified several that have consented to be in the study; actually three to date. And as I said, we're continuing to enroll subjects. We've also recruited our negative volunteers. So these volunteers 002, 004 and 005, those are hepatitis B infected individuals. You can see
that there's a range of 10 to the 6th, 10 to the 8th in terms of viral load. All the down stream samples from the left and right deltoids have been negative for presence of hepatitis B DNA.

So we believe that this is a very powerful method to demonstrate cross-contamination safety with human volunteers focusing on the infection of interest, hepatitis B infection and using a very sensitive method for that detection.

Next slide.

So from that pilot study our plans are to then proceed to a larger scale study that would be conducted in China. The reason for that is that in China there is a very high prevalence of hepatitis B infected individuals, more so than in the United States. There's also a higher prevalence of higher titer individuals. And so we think that it'll be much easier to recruit those individuals and then add to the safety profile for the technology.

The current study design is focusing on recruiting 300 high titer volunteers. Each volunteer would receive two injections. So it would have a similar design to the pilot study. We're using the same assay, and so the jet injector down stream samples that are generated in China will be shipped to NGI for analysis.

The location will be in the Beijing area. And there are three sites, three hospitals that are focused on hepatitis treatment that have agreed to participate in the study.

And we're working with a clinical research organization. It's an MDS Pharma
office based in Beijing who help manage and coordinate the study working together with PATH and Felton International.

And I'd like to close by saying that the data that's generated, we plan to submit that in a submission to a national regulatory authority, perhaps it's the FDA, perhaps it's the Chinese SFDA. And we were very supportive of the FDA's efforts to determine a pathway to demonstrate safety of the technology. And we offer our assistance to help work with your group to determine a way forward. And we firmly believe that there can be a way forward to demonstrate that the technology can be safe.

With that, I'd like to introduce Dr. Mark Kane, who is my colleague at PATH. And I would say that he is a hepatitis B expert. He would like to make some comments regarding earlier points that were made this morning.

Thank you.

DR. KANE: Thank you.

These are more observations of things I've heard today and don't represent in anyway any kind of official industry stance, but just some comments that I had. I didn't know where else in the program to be able to insert them.

I think in 1984 by necessity, because of the level of technology and understanding, the issue of transmission was defined as a volume ---

CHAIRMAN EDMISTON: Excuse me. You're not on the list that we had here. But I appreciate your being here. But could you make
some statement in terms of possible conflict of interest?

DR. KANE: Okay. My name is Mark Kane. I work at PATH, so I have exactly the same conflict of interest profile as Dr. Zehrung. Also worked for 20 years in the hepatitis branch of the Centers for Disease Control, the last ten of which at the World Health Organization.

CHAIRMAN EDMISTON: Thank you.

DR. KANE: Okay. I'm sorry.

As I said in 1984 the issue is framed as a volume issue in terms of picoliters of blood that may or may not be infectious, but we're way beyond that now in our understanding of how many genomes and viral particles might be in a ejectate. And so I think it is possible to ask questions like given any level of detection in a test system what is the probability that there's one infection dose in that ejectate. And it seems to me that the sensitivity and specificity of some of the tests that we've seen discussed this morning would make that an answerable question in the real world.

The second issue is that I haven't heard any reference to the experience with blood screening using the ELISA test, which is approved by FDA for use in screening all blood. I understand that certainly there are many differences between the problem of preventing post transfusion in hepatitis, but there are also are some interesting similarities. And certainly infusing an entire unit of blood versus the volume of an ejectate is relevant, too.
And basically, using an ELISA which has a sensitivity of hundreds to thousands of picoliters equivalents has essentially eliminated post transfusion hepatitis B in the United States. I think the latest estimate that I've seen from NAHS that residual and we may be getting down into compliance error problems is about 1 transmission for 220,000 blood transfusion.

And so we have a test of orders of magnitude less sensitivity than the current tests that are available that have essentially done in a public health sense a very valid job in reducing the transmission of disease.

The next point has to do with the model that Martin presented. And when you present a model, when you multiple the worst case scenarios for every variable in your model, in this case probably ten, and present that as the results of your modeling, I wonder whether a better way of presenting a model is to take your best case estimates for every variable, multiple them together, present that as the outcome of your model. And then you can use the worst case scenario and even best case scenario estimates as a sort of confidence interval. Because it seems that the greater probability is that the amount of transmission that would occur using our best knowledge of what those variables are would be very, very much lower than the model that was presented to the Committee by Martin.

And the position of WHO puzzled me. In a sense we were told that there are 12 to 16 billion injections given int he world. That 50
percent of them were estimated to be unsafe. Immunization injections account for less than 5 percent of those 16 billion injections. And they're pretty much the only ones that use AD syringes. The other 95 percent of the 16 billion injections rarely use any AD syringes, yet the WHO position is that they cannot recommend the device with any theoretical risk of transmission because if all needle injections were given compliantly, there wouldn't be any risk. To me this seems really a lot like the perfect being the enemy of the good. And I wonder if this Committee would, you know, consider the realism of that.

And that's really all I have to say.

I think that there is a way forward, given our knowledge of the infectivity of hepatitis B and the current sensitivity and specificity of some of the tests that had been presented this morning. And I think that as I imagine a scenario and a very bad weekend when 300 million Americans need to be injected, and doing that with 300 million single dose vials of vaccine with needles and syringes seems to me a very unlikely scenario. So I think that there is a potential in this country for a useful high load jet injector device. And definitely for mass campaigns in the developing world.

So I would thank the Committee very much for the opportunity to address you. Thank you.

CHAIRMAN EDMISTON: Thank you. At this time I think that there are other public speakers, other speakers from industry who would
like to comment. But because these two individuals that have represented a single entity, I'd like to take a few moments now to ask the Panel if they would have any specific questions for these two gentlemen. Yes, Dr. Butcher?

DR. BUTCHER: Yes. I just wanted to make sure when the presentation was being made and I understand we didn't see the video, but is what happens this is what you passed to us, this is taken off each time and is this disposed or is this sterilized and then a new one put on with every injection? Is that --

DR. ZEHRUNG: Yes. Once the injection is provided into the patient, then the device is reset. So the device ejects that spent protector cap, and then that's discarded. And then a new sterile cap is placed on the nozzle face.

And you can see in the packaging, actually the packaging comes in a tray of 25 protector caps that can be broken into rows of five protector caps. And so I passed some of the pathing examples around.

You would present or open one tray or one protector cap at a time, place it on the nozzle face of the injector, provide the injection, eject that spent protector cap and then open a new sterile protector cap and place that on the nozzle face again and proceed with injections.

So for that, you know the process actually explains why the rate is lower than the
900 an hour or whatnot that we've heard with the earlier MUNJI devices.

Does that answer your question?

DR. BUTCHER: Yes.

CHAIRMAN EDMISTON: Dr. Word?

DR. WORD: I think I have two questions, and I think I just need clarification.

From an industry perspective, and I think you partially answered it, when I looked at where you've done your mass campaigns, you've been administering things such as meningococcal vaccine, yellow fever and polio. Polio is eradicated here. We don't have meningococcal, we're not in the meningococcal belt. And we don't have yellow fever. So essentially what the message I'm hearing right now, because in the beginning I wasn't sure what the question was and it sounds as if this isn't something that you want for use in the United States, but you're looking for use outside. So then my question really is what is it that you're asking this Panel to do? Because why wouldn't it be for their regulatory agencies of that specific country?

You've alluded to the fact that oh we might go to China. We're interested in hepatitis B, etcetera. What question do you have, and I'm not quite sure. Are we here just to provide advice? Because everything that you've said I don't see where this is going to be utilized here.

DR. ZEHRUNG: Right. Well, actually, I think that -- let me clarify again.
I work for a nonprofit organization, so I'm not an industry representative in terms of being a representative for the manufacturer. Our focus is health in a developing world. And so when I listed those mass immunization campaigns, those are examples of applications for this technology, at least as we see it. But there is also the potential application for bioterrorism response or pandemic response in the United States. That's something that we are interested in, but as PATH as an organization that's not our focus. That's not the constituents that we focus on.

But going back to the FDA meeting that was held last year, I think one of the recommendations from that Committee was that WHO deferred to national regulatory authorities in terms of determining the level of risk and safety of the technology. So at least for the United States it's the FDA.

For China, for instance, and we have already initiated discussions with Chinese CDC and a specific program, immunization program representatives of China. We'll work with their NRA to license this technology in country working with the manufacturer. So we will be doing that individual country NRA submission and interaction. But at least for the United States, the question is as the Panel has laid out, is it safe for the United States, what are the methods that could be used to demonstrate safety. And, again, we defer to the FDA and the Panel to determine that, at least for the United States. The United States is an example around the world
in terms of national regulatory authorities. And many regulatory authorities would follow the FDA lead in terms of demonstrating the safety of the technology, and there are many examples of that.

So I think there is a connection, although as you say the focus for the FDA is consumer protection in the United States.

So I hope that answers--

DR. WORD: I guess, too, in all fairness for the FDA is it fair to have them review and do all the work and not be compensated for it, for something that's going to be utilized in another country? That's why I'm saying it may meet -- like there are standards that will be set for our government, but it may not be the same for the others. And that's why I'm saying is it not appropriate that you go to their regulatory agencies and find out what's appropriate and acceptable for that particular country? I mean, it sounds like you want them to do the work and not get compensated.

DR. ZEHRUNG: No. I think that it's a combination of two approaches. I think that direct country level interaction, which there's a different risk benefit profile that they'll evaluate versus application of this technology in the United States. So if the FDA can determine what that risk benefit profile is and if it is appropriate for use in the United States, that is information that would feed into a decision for a local or like a country level NRA. Perhaps they won't agree with that.
Perhaps they would agree with a different risk profile calculation.

So it's a combination of the two approaches, I think.

CHAIRMAN EDMISTON: Ms. Petersen, do you have any questions?

MS. PETERSEN: Yes, I had a couple of questions.

First, with regard to the information about speed. The presentation notes that the injector will do six injections per minute. Does that include the time to eject the used cap, to --

DR. ZEHRUNG: Yes.

MS. PETERSEN: -- open another new one to put it on?

DR. ZEHRUNG: Yes. We've conducted time studies in terms of using the device. And with a proficient user, someone that's trained, they can achieve the six injections a minute rate. So it includes placing the protector cap on, filling of the dose, provide the injection, rejecting the spent protector cap, opening the package.

MS. PETERSEN: And will the unit operate without a cap?

DR. ZEHRUNG: The current design -- well, actually the design that was cleared for market last year did not include an interlock feature. The current design that will be actually used in the China safety study will have an interlock. And so that it will require placement of the protector cap on the nozzle face for the device to operate.
And it was part of this sort of the development pathway that felt, and then perhaps Dr. Loskutov could speak to this, first demonstrating safety in a small pilot study and then having that converge with the design development effort to include more specific safety features such as this interlock prior to actual market introduction.

And I should say that these technology is not being sold. It's not being used in the world. We're actually working with the manufacturer to build the safety profile. And we're looking for NRA approval and also public health agency approval for use of the technology. So it's not really being used. It's not delivering vaccines at the current time. We're conducting safety testing.

Is that --

MS. PETERSEN: And will the newer version with the prevention capabilities so that a AP has to be used, will that be fairly easy for an individual to modify so that caps are not necessary? I guess what I'm saying is can someone buy it and then get the safety mechanism off the gun so they can use it without caps?

DR. ZEHRSNG: Well, I think the focus of the design effort has been to implement an interlock feature that's very durable that would be very difficult to disable. Now, with tools or whatnot, it perhaps may be possible. But we've been focusing on and working with the manufacturer to develop a feature that would be as durable and as effective as possible.
And if you'd like to learn more, we could perhaps demo the device for you. But that's been the focus. And actually that was a concern earlier on pre-WHO safety meeting last year working with Dr. Bruce Weniger and also Dr. Mark Friede at WHO that an interlock feature was an absolute. If this device was going to be used in the developing world for mass immunization campaigns, it needed an interlock. So we've been focusing on that as an effort.

CHAIRMAN EDMISTON: Dr. Word?

MS. PETERSEN: Do you have any sense of the cost of the caps? Say the device approved and sent out for use, what the caps would cost?

DR. ZEHRUNG: That's a good question. The spec has been that the cost per injection needed to be much less than the cost of an auto-disabled needle and syringe, at least in the developing world. So the cost of auto-disabled syringe is, perhaps, down to .04 cents, more likely .05 to .06 cents range. It's been projected that the cost per injection for this device with the disposable protector cap would perhaps be .01 to .02 cents. So that's another benefit of the technology; that it's extremely low cost. And not only is it needle-free, but it's comparable to -- well, actually it exceeds the auto-disable syringe costs, but it's comparable to reusable syringe costs. So that was another spec that we focused on.

MS. PETERSEN: And how does that cost compare with prior MUNJIs, the cost of use?
DR. ZEHRRUNG: Well, prior MUNJIs did not have a disposable component. There were some components that needed to be replaced in terms of O rings and whatnot, but those devices -- and I can think of an example of like the Ped-O-Jet, which was perhaps $2,000; the per injection cost amortized over the life of the device was very low, fraction of it essentially. So it is more expensive than those earlier devices, but the reason for that is that there is a disposable component, which is a recurring cost per injection.

MS. PETERSEN: Sure. But in developing countries would not the practitioners be comparing the cost of the previous device with the lower cost to this new one that has the additional cost associated with the cap?

DR. ZEHRRUNG: That's a good question. Interestingly enough, given the stop of using this technology in the developing world, there's been a turnover with those health care workers, many of which are not familiar with jet injectors. Those health care workers have either retired or they've gone on to different parts of their life. And so when we've interacted with health care workers in the developing world, you know their first question is where is the needle. So that's part of also our challenge is really reeducating in terms of the benefits for needle-free injectors, be it this device or disposable cartridge injectors, as Dr. Friede had talked about. And so there isn't that comparison.
Actually, the health care workers that we've talked to, and also program managers, their question is safety. They want to know that it's a safe technology. They're concerned about speed, they're concerned about using the device in terms of the logistics of cleaning and sterilization. They focus more on that.

Many times it's not those health care workers or program managers that control the money. It's actually further up the chain. So there's a difference there. So there isn't that comparison that's being made.

CHAIRMAN EDMISTON: Dr. Layton?
DR. LAYTON: Yes, I have several questions. One relates to the bullet point where you say prevents cross-contamination.
DR. ZEHRUNG: Yes.
DR. LAYTON: And can you say that it prevents splash back?
DR. ZEHRUNG: That is prevents splash back? Splash back occurs, the protector contains that splash back and then that's discarded. So splash back does occur during in the injection into tissue, but that protector cap contains it. So the splash back does not contact the nozzle face and then thus the fluid path.

DR. LAYTON: So it prevents splash back to the fluid path way in the nozzle?
DR. ZEHRUNG: Right. So there is a reusable fluid path and the nozzle orifice that generates the high velocity narrow injection stream, that stream passes through the protector cap and into tissue. So the injection site
splash back or reflux is contained within the protector cap.

DR. LAYTON: All right. Next question, is this -- you've only presented information on subcutaneous. Do you have anything on intramuscular?

DR. ZEHRUNG: That's a good question.

Our focus has been as a design spec given the prevalence of subcu or vaccines that are delivered subcu for mass immunization campaigns, we would consider testing with an IM specific nozzle if that were requested. But I do not have data on IM delivery.

DR. LAYTON: All right. Thank you.

The final question is either you or the FDA, possibly. You said you have a special 510(k) and the label says that it's an IDE. Why? Why was --

DR. ZEHRUNG: It's IEE.

DR. LAYTON: Why, if says an investigational device, limited by U.S. And you said it was a special --

DR. ZEHRUNG: Oh, the packaging for the protector cap. These are actually samples that I passed out. So I'd have to defer to Dr. Loskutov and Felton International in terms of describing their current labeling and instructions for use. But I just passed those out as samples.

DR. LAYTON: There was a 510(k) --

DR. ZEHRUNG: Yes.

DR. LAYTON: -- for this protector cap.
DR. ZEHRUNG: Actually, there is an original 510(k) for a device called the BI-3M, which is precursor to this technology. It utilized a different protector cap. And actually, the Russians over the last 15 years had identified this as a needed and started with very crude protector cap designs, and it's been refined over the years.

So that original 510(k) was the basis for the special 510(k) that was cleared last year.

DR. LAYTON: All right.

DR. ZEHRUNG: For this new device iteration.

DR. LAYTON: All right. Thank you.

CHAIRMAN EDMISTON: Any other questions from panel members? Dr. Word?

DR. WORD: Just a question about this cap here. You said it can't work without it, correct? What happens if someone just forgets to take it off and change it between the patients? I mean, is it designed that it only can work one time?

DR. ZEHRUNG: Yes. The interlock feature requires that the user follow all the steps for filling and ejecting the spent protector cap. So you could not use the cap or use the injector again with a spent protector cap. It would force the user to eject that spent cap.

CHAIRMAN EDMISTON: Dr. David?

MR. DAVID: Thank you. I have a couple of questions.
One, is you design associated with specific volume that the cap is protecting or it's a general statement you have on your product?

DR. ZEHRUNG: Volume in terms of splash back or --

MR. DAVID: In the injector?

DR. ZEHRUNG: Oh, you mean the fixed dose? Again, that's a spec that was determined by the volume that's delivered in mass immunization campaigns, which is basically -- I mean that's a fixed dose that's used in immunization programs as well as in immunization campaigns. So other than perhaps BCG, all vaccines are delivered a half cc.

MR. DAVID: You mentioned sensitivity and specificity. I didn't information relating to specificity.

DR. ZEHRUNG: Of the Hep B DNA tests or --

MR. DAVID: On the fluorescein.

DR. ZEHRUNG: The fluorescein test? Well, actually, it's a very specific test. And we have a report that we put together that I could provide to you and the other Panel Committee members that goes into greater detail describing that test.

MR. DAVID: My last question relating to user skills. And I think you've described it as logistics; things that involve with cleaning, sterilization and maintenance of the device. The cleaning and sterilization, your study included that just as part of a validating study particle or that's a requirement?
DR. ZEHRUNG: It's a requirement. It was a requirement, actually, from the IRBs that review the study protocol. And we conducted a test to demonstrate that the fluid path can be effectively steam sterilized. Through a third party laboratory we conducted bioburden testing introducing bacterial contamination into the fluid path, following the cleaning procedure in this and then also the sterilization procedure to demonstrate that the fluid path post steam sterilization is sterile.

So not only is it a product requirement in terms of maintenance and demonstrating the device, the fluid path can be sterile, but it was also an IRB requirement to allow for approval of the study.

MR. DAVID: And how often would you recommend to do that?

DR. ZEHRUNG: It really depends on the usage, and actually that's another design development effort that we're undertaking determining what the maintenance life and cycle life would be for the technology. I think that earlier devices there was this recommendation for daily sterilization. We are determining study designs to demonstrate if after using a particular vaccine, such as measles vaccine, for several hours would the user have to replace that fluid path and use a new sterile fluid path.

And actually I didn't mention this, but the idea is that with one injector hand piece and foot pedal there would be multiple fluid paths. So in a centralized facility, you
would sterilize perhaps five, six, half a dozen or more fluid paths and then that would be packed with the injector and then sent out for injections on site.

So if a fluid path, either there was a malfunction or if by our study results we demonstrate that it needs to be replaced more than daily, then the user would then take the old fluid path off, put a new sterile one on. And those sterile fluid paths, the intent is that they would be packaged within a tyvek pouch, so then they would be sterile to the point of use. Once the user is ready to use that fluid path, they would open the pouch up, install it on the injector, prime the fluid path and then proceed with injections.

MR. DAVID: Your mechanism, the interlock that you mentioned, so do you have any estimate on a life cycle, how many uses?

DR. ZEHRUNG: Well, our target in terms of durability of the device has been a quarter million injections. We have conducted some initial life cycle testing, and that will be part of the design verification work that will occur with the latest design iteration to verify that the design does meet that design requirement prior to any introduction in the marketplace.

MR. DAVID: Thank you.
CHAIRMAN EDMISTON: Any further questions by the Panel?

Thank you very much.
DR. ZEHRUNG: Thank you.
I understand we may have one or two other presentations from industry representatives. Do we have any further industry representatives in the audience? Raise your hand, please.

We have two? Could one of you come forward first and identify yourself? And, again, briefly describe any potential conflict of interest?

MS. D'ANTONIO: Yes. My name is Linda D'Antonio. The name of my company is DCI. And in terms of conflict of interest we're a needle-free jet injector manufacturer. Not manufacturer, developer. We are working on disposable cartridge needle-free jet injector.

And, actually, I wasn't planning to speak today but I just wanted to address one point. This morning I think it was during Martin Friede's presentation, there was a question that came up about high speed devices and the multiuse nozzle jet injectors. And I just wanted to make sure, to make clear that there are other high speed needle-free jet injectors, those being the disposable cartridge type, which is the type that we're developing.

Our company is developing a high speed disposable cartridge jet injectors for mass immunization type use, for use in the military for bioterrorism, preparedness kinds of things response. And so I didn't have really more to say than that, other than just to simply make it clear to the panel that there are alternative injection systems to the multiuse nozzle jet injectors.
And I don't know if my colleague has more.

So if there are any questions on that, I would be happy to answer them. But just my clarification.

CHAIRMAN EDMISTON: Thank you.

Yes. Come forward and please identify yourself. Again, identify any conflicts of interest.

MS. CALLENDER: I'm Kathleen Callender from Genesis Medical Technologies. And we developed the Pharma-Jet injector and our disposable vial.

I am President of the company, so I do have an economic interest in it. Our family owns the majority of the stock.

And it's kind of been my mission to do this. I've been working on it for probably eight years.

Mine is completely disposable, and it's a one time use plastic polypropylene vial. So our concept is to prefille it and to booster pack it for ease in use in third world countries as well as in our grocery stores and our flu vaccine clinics.

And we have been marching through the FDA, and got a long way to go. We're cleared as a Class II medical device, but now I understand I have to go through the Office of Combination Products.

So I just also wanted to let you know that there's some other people out there that are trying to solve the problem of disease
transmission and trying to get rid of some of the needles in the world.

Thank you.

CHAIRMAN EDMISTON: Thank you.

Are there any further comments from industry? If that's the case, let's move on.

I would now like the FDA to present the questions to the Panel. I'd like the questions presented in total, and then we'll go back and discuss each question individually.

MR. LIPMAN: The first question is: Identify the scientific questions that need to be addressed to demonstrate whether MUNJI devices are safe for multiple patient use in the United States.

Second, discuss the adequacy and feasibility of the currently available methods to assess the potential for cross-contamination and the risk of disease transmission by MUNJI devices.

And finally, Feinman, et.al. in 1984 suggested that a volume of blood as small as 10 picoliters can transmit hepatitis B virus in chimpanzees. However, this finding is based on a single animal study. Considering the potential public health benefit of MUNJIs is there a threshold of volume of blood contamination that presents an acceptable risk? If so, what threshold would be considered acceptable?

CHAIRMAN EDMISTON: Okay. Could we go back to question number one. And let me comment before I open this to the Panel that the issue at hand is really the issue of safety and cross-contamination. We're going to address the
issue of whether or not these devices are safe. And if we have an issue regarding the safety of these devices in terms of cross-contamination, then what the technologies or the tests that must be applied to validate their efficacy?

Again, the first question: Identify the scientific questions that need to be addressed to demonstrate whether MUNJI devices are safe for multiple patient use in the United States.

And this time I'd like to open this up to the Committee, the Panel for any commentary. Yes, sir, Dr. Butcher?

MR. DAVID: Mr. Chairman, the thing that I would like to ask is that we have a definition of the MUNJI devices now. We've been presented with a few hybrids or alterations or advances and all like that. Is all of that going to come under the MUNJI device or we just sticking with MUNJI?

CHAIRMAN EDMISTON: We're focusing on multiple use devices.

MR. DAVID: Okay.

DR. ARDUINO: Well, I might as well start.

I think if you look at most of the studies, we're looking at a poor surrogate of blood contamination. So instead of focusing on blood contamination with the testing that is available now, supposedly molecular testing for DNA, we should be actually doing more studies to look at to see if we actually have virus carry over in your injections or cross-contamination that way. Because I have problems with using
serum albumin. It's just too much of it could be leaked to too many false positives. And if you look at some of the studies, even their negative control -- you know, some of the negative controls were positive with those as using that. Or we have to find some other indicator of blood contamination there.

So I think we should be looking at the infectious agent.

CHAIRMAN EDMISTON: Any further comments?

DR. BUTCHER: Well, again, my comment if to follow along with what was just said, is that it seems as though all of the studies that we listened to were previous studies and none of them seemed to be updated and so forth. So it looks as though we're going to really need to have some concurrent studies as to what's going on.

CHAIRMAN EDMISTON: Dr. Layton?

DR. LAYTON: Yes. In terms of scientific or engineering questions, I think you definitely have to put some definition in to the three different intended uses. And what I'm saying that is intramuscular or intradermal or subcutaneous may all require different volume ranges, different pressure ranges. And these are going to play a role on the amount of splash back and also the amount of potential contamination. So definition needs to be established relative to what those performance criteria are for those three different applications intended use.
CHAIRMAN EDMISTON: Let me ask this question and toss it out to the Panel: Do you think that there is sufficient risk in the use of these devices that warrant consideration of whether or not these are safe devices as they currently exist?

MS. PETERSEN: I think it may be that if we provide recommendations, we want to create recommendations that take into account different scenarios under which they might be used in the United States. You know, we keep hearing about the bioterrorism, and if you had to vaccinate 3,000 people or 300 million in a weekend how would you do that? And that's certainly one scenario. And at that point we would be willing to accept some level of risk that I suspect is very, very different for wanting to vaccinate the 1500 first graders in some given town. And it's handy to do it one day and kind of have it over with, but that's not a pressing need. You know, if Junior can't be there Tuesday afternoon between 1:00 and 4:00, it's not going to be a problem if he's there Friday morning or next Wednesday.

What would be okay I think is very different in those two scenarios. And there's also the question of how the military component fits in as well. Because, presumably, that's not quite the same thing as the bioterrorism scenario.

CHAIRMAN EDMISTON: So what I'm hearing from the Panel members based on not only the information that was presented but the information that wasn't presented, is that there
is a relative level of risk of cross-contamination with these devices. And that either through increase in technology or through possibly considering alternatives from these devices, this is the direction we should be moving in. Is that correct? Is that a fair assessment?

MS. PETERSEN: Can we quantify the risk associated with the various types of MUNJIs and compare that to other possible devices and tie that into how it can be used?

CHAIRMAN EDMISTON: Well, I think you brought up a very good point. And where I'm uncomfortable is that in looking at how these devices are being used is to assess the risk, the true risk associated with the use of these devices. And while I've heard some compelling information based on both personal and laboratory experiences, I'm not really sure from the epidemiologic perspective. I have a good handle in terms of what the true risk is in the use of these multiple use devices.

I would personally like to see some additional data developed looking at the epidemiologic nature. And I think that data is available in a retrospective perspective to determine what the relative risk is.

Now, that's a sort of a personal perspective working in the area of hospital infection control. But does the rest of the panel sort of have a similar concern?

DR. ARDUINO: Well, some of the EPI study, or there's potential EPI studies to actually go -- if we look at, say, the VA and
the data they have with their elevated anti-HCV rates. If we were able to go back and look back to see okay, now what were the exposures, are there other compounding factors involved. And actually do some sort of formalized study that actually then will put okay, we have these risks associated with these -- well, is there a risk with a certain type of device or is it just the categories itself or are there other compounders in there?

CHAIRMAN EDMISTON: The reason I bring that up is that in every device which is approved by the FDA is a package insert. And that package insert has a practice in terms of how that device should be used. And every device has potential for being abused.

And I think we've had commentary from some members of the audience has suggest, this should be fail safe device. I don't see that occurring with the current pre-amended devices that are currently in the market.

So I think what I would like to see personally from my perspective is some sort of epidemiologic data to really give me a sense of what the true risk is within both U.S. populations and the populations that are Dr. Friede is dealing with from the World Health Organization.

Dr. Lin, is that a reasonable question to ask?

DR. LIN: Well, that's your call.

CHAIRMAN EDMISTON: Well, you have to do the work, all right.
The other issue, this is sort of -- Dr. Word?

DR. WORD: I'm sorry. As you started to begin to break down the various scenarios, which I think is very important, I'm still not quite sure if we utilize these same -- you use these MUNJIs in adults versus pediatrics, do I take a 2,000 gram infant versus a 50 kilogram adult, I mean -- I don't know if you've looked at them in that population. I assume you have. But I would like to see something in terms of pediatric versus adults and break it down. Because most children are immunized by -- they receive the majority of their immunizations in the first two years of life when they're receiving them. So if you're saying -- it sounds as if we're utilizing in the United States, it would be during a situation where we would have to have a rapid mass campaign, and that would really be limited to some type of bioterrorism type of thing. Because if we had a pandemic with influenza, we wouldn't have the flu vaccine available. It wouldn't be made anyway, so you couldn't administer it. No one could make it that quickly. So you're looking at something different.

But I also like your comment about why not test it not to look about see if you isolate viruses. So I would second that and also just looking at the route that it's administered.

CHAIRMAN EDMISTON: I think your comment would become appropriate as we move down to the second and third question.
DR. WORD: Oh, I'm sorry.

CHAIRMAN EDMISTON: The issue that you raise is the relative safety of these devices, these multiple use devices in pediatrics versus adult population.

If there is an issue of safety, and we're talking about cross-contamination now when we use the word "safety," then I suspect what I would want to know is there technology available which would allow you to retrofit, for instance, the pre-amended devices? I think this is a compelling argument for using multiple use devices, but again it doesn't address the pre-amended component. And I think that's an issue we have to lay on the table because there are probably thousands, if not hundreds of thousands of these devices still out there.

So is it possible to develop technology either similar to this or parallel to this that would make these pre-amended devices safe? What's the thoughts on that?

MR. DAVID: I agree with you, Mr. Chairman. I also would like to add to the scientific and Terry said correctly the engineering question is also looking at the life cycle. If we're talking about high pressure, high flow devices it will be appropriate to look at benefit risk ratio when the device is used for 100 thousand injection as compared to the first or the second injection. And what is the performance effect of that? And that question does not have an answer today.
CHAIRMAN EDMISTON: And does the risk decrease or increase with longevity of the device?

MR. DAVID: Right. Correct.

CHAIRMAN EDMISTON: Are there any other comments relative to that first question? Let me review that again; is there data available on the relative risk of these devices within both U.S. and world population? That would be important information to have from a scientific perspective.

Number two, what data exists looking at the safety or the potential for cross-contamination of these devices between both the pediatric and the adult patient population?

Number three, if there is indeed a risk, what technology is available that either is in place on new devices prior to approval or in devices that could be retrofitted to the devices already that have been approved through pre-amendment?

And the fourth, which is an interesting consideration, is that as these devices age is there any data to validate the safety component of these devices as they move through their life expectancy of 100,000 or 200,000 injections?

Dr. Lin, is the FDA satisfied with the response for that first question?

DR. LIN: Well, you want to put me on the spot.

CHAIRMAN EDMISTON: You're sitting at the table.
DR. LIN: Yes. I think this is probably is a very course of this and then the recommendation.

CHAIRMAN EDMISTON: Having gone through this once before, what we've been presented with today at least in my mind has given me a better concept of how we can crystalize some of these answers that we couldn't do six years ago.

DR. LIN: Yes. But you looked -- the bottom line of our question essentially that, for example, today or tomorrow a manufacturer present, such as one we have, but any new generation device come to us, then you remind when we talk about fond memories, what type of an issue we should ask the manufacturer to address other than, you know, we know that this is some potential, whether it's perceived or it's real or a close combination. But what type of question we should ask. I think you point out -- that's probably beyond what the pre-market review we can do. But if somebody come to us, as I say, either today or tomorrow or in the next few months, what type of questions, scientifical question we should ask in view of those potential cross-contamination. You can help with, that would be assuming --

CHAIRMAN EDMISTON: Any more comments on that first question? Let's move on to the second question.

DR. WORD: I know you've asked about cross-contamination. Are you asking us to specify what specific agents that we're looking for?
DR. LIN: No. I think it's scientific equation for some part right now.

DR. WORD: Okay.

DR. ARDUINO: Or the type of testing? Are you kind of aimed at, you know -- we know that splash back is a problem. What type of testing have you done to show that the device does not get contaminated.

DR. LIN: Right.

CHAIRMAN EDMISTON: And this is from the manufacturer's point of view.

DR. ARDUINO: From the manufacturers.

CHAIRMAN EDMISTON: Because they're going to be responsible for conducting these tests.

DR. ARDUINO: Yes.

DR. LAYTON: That's the questions that the FDA asks.

DR. WORD: Okay.

DR. LAYTON: Because they're asking those questions relative to industry. And a lot of them is how much splash back does your new device have and how does that compare to the predicate device.

DR. ARDUINO: And if there is splash back, what engineering controls have you included your design to prevent contamination of the fluid pathway. Kind of wind that up.

CHAIRMAN EDMISTON: Yes. That works well for the new devices coming.

DR. LIN: New devices, yes.

CHAIRMAN EDMISTON: But it doesn't address the pre-amendment devices. And I suppose
we could take a position right here that these multiple injection devices are totally unsafe and they shouldn't be used at all. But I haven't seen the data that compels me, at least from my perspective, to agree with that. I mean, how do you feel about this as a Panel?

MR. DAVID: I feel that you definitely raised the correct question, and that's not only we looked at -- reassociated with data that was presented, but data that was not presented concerning. And my feeling is that definitely we need to send a message of cautious --

CHAIRMAN EDMISTON: It may very well be that based on these initial questions that we proposed, especially the first question, is that the risk is significantly high in selected patient populations. And based on that, then possibly these multiple use devices may not be safe. But I don't think we have that information at hand to make the decision, or even to make that recommendation to the FDA.

DR. LAYTON: No. I agree. We don't have. But it's suspect.

DR. WORD: So would you consider any -- say if you cultured, you did a viral culture or PCR, whatever, and you isolated any virus, would that be considered unacceptable? Because if I -- you know, if it's 1 in a million cases that it happens, if you're that one it becomes important. But then, too, I may be willing to take 1 in a million, just like with a lot of vaccines that have adverse effects, you have to do a million people in order to see it to
protect the good. So then if you limit it back to the scenario that you would utilize it in the United States, then you might say, you know this is worth it.

CHAIRMAN EDMISTON: You make an excellent point. Because it always comes down to risk versus benefit. And it may very well be the vaccine itself has greater risk associated than actually the injection component. So, there's a lot of data we don't have here and hopefully we can develop some of this data over the next couple of years.

DR. LIN: Well, but you know we probably cannot wait for another couple of years. But, as I said, if the device come in, then what -- for example, present some of their test data. For example, they have a study or have a full test, unfortunate that data is not available yet. But now that the question -- the submission come to us and not -- like today or tomorrow, then in your mind that as our FDA Advisory member, what would you advise the FDA, what type of scientific question would you ask?

For example, as Dr. Wood point that maybe you have limited to certain patient population or those type of questions. That's what we are looking for, your recommendation.

CHAIRMAN EDMISTON: Yes?

MR. WATSON: I just wanted you to put yourself in the reviewer's position. You're sitting at a desk, somebody drops this on your desk and says, you know, evaluate this. What question would you ask of that manufacturer. And
I think you were going that route. I think I heard some of the comments were heading now scientific testing, that kind of thing. That's really what we want to know. Because we're in the situation where we will see more, probably. And we want to make sure we're at least asking the right question, realizing that maybe we don't have quite yet the cut off levels, if you will. Maybe that will come later. But having some appropriate questions to be asked will give us a good starting point. And I think you started down that road. So I just wanted to encourage that.

CHAIRMAN EDMISTON: Well, we know splash back occurs. We know it occurs. And we know that there's a risk associated with that. We don't know how significant that risk is. One tack you might take is that devices that are being submitted have to have the ability to reduce the risk of splash back. And that would be a reasonable expectation understanding that splash back is a risk. So that fits into that technology component; what technology is in place or can be placed, input in place with that device, these devices that are coming along to reduce that risk of splash back.

DR. LAYTON: But it has to be expanded to the extent that the splash back is also over the performance characteristics of the device. The pressure variation that the device sees, the shelf life or the number of uses. Also the volume that it injects.
So splash back has to be looked under all of these conditions. Splash back leads to contamination.

CHAIRMAN EDMISTON: So in devices presented to the FDA, whether it's ID subcu or intramuscular, that there has to be some performance criteria to demonstrate that there is a reduction in splash back?

DR. LAYTON: Yes.

MR. DAVID: I'm a little bit hesitant with the word "reduction." Reduction from 1,000 to 999.

DR. WORD: You have to define.

DR. LAYTON: Reduction from the predicate device, for one aspect of it. If you have a predicate device to demonstrate, to be able to compare it to. But the other aspect is, you know, just having the information on splash back and relating into our next questions that we're addressing provides a tremendous amount of information for them to help make a decision.

CHAIRMAN EDMISTON: Any further comments.

DR. WORD: I guess I, too, am a little concerned about that word "reduction." Because it's non specific. I mean, they could down by one percent, it would be reduced. So I don't know how -- I mean, quite honestly maybe I missed it or I don't recall anyone quantifying how much splash back if you had. If they quantify how much splash back that you're getting now from the one that you have -- you know, I don't know if someone picks an arbitrary letter -- I mean, amount. I mean, do you go
down by 15 percent, do you go down by 25 percent? I mean, you're setting a goal for something. Or something realistic.

CHAIRMAN EDMISTON: Well, let me do this: Let me bring Dr. Friede, can you stand up by the podium. And I could I bring in the gentleman from PATH, could you stand up next to him, please?

Here's the question. I'm going to ask the question from the gentleman from PATH. When you designed the system what was the percent reduction in splash back within your system?

DR. ZEHRUNG: The goal was complete elimination of splash back in terms of the contamination of the nozzle and the fluid path. In comparison to predicate devices such as the Ped-O-Jet device and the earlier design. Like, for instance, the fluorescein test, we used a threshold of 10 picoliters, anything below 10 picoliters was considered not contaminated, anything above was contaminated. And the tests that we conducted in comparison with the predicate device was to demonstrate that at that definition of contamination, the device was free of contamination.

CHAIRMAN EDMISTON: So you achieved greater than 95 percent reduction?

DR. ZEHRUNG: Yes. Yes.

CHAIRMAN EDMISTON: Dr. Friede, let me ask you a question. With that expectation what's your thoughts on a multiple use device or a criteria for the development of a new multiple use device that would assume a 95 percent
reduction in splash back, be it IM, ID, substitute, subcu?

DR. FRIEDE: I think seeing the fluorescein data, this is the first time that we have seen a test that appears to be repeatable, reliable, to the extent that this does not require very, very complex technology that can only be performed in one laboratory on earth.

So as a benchmark I would say this is beginning to look like a very good benchmark.

The only concern that I would have as a scientist, and this a personal view, is that we do not yet know how the in vitro splash back is comparable an in vivo splash back. But I think this is the first time that we have seen a test which shows really significant reduction.

Now to put numbers onto it, I don't know. But when you look at theirs, it is zero contamination using the most sensitive measurement that we have ever seen. So this appears to be a very good benchmark.

CHAIRMAN EDMISTON: Well, let's hold that assay component thought for a moment when we get to our next questions. But in terms of a percent reduction, this Panel has been asked to make recommendations to the FDA. Do you feel that a greater 95 percent reduction in splash back is a reasonable expectation given the current level of technology that's emerging with these devices?

DR. FRIEDE: The data that was presented by Darin suggests a 100 percent reduction in splash back.
CHAIRMAN EDMISTON: So you're recommending that we suggest to the FDA that there should be a 100 percent reduction in splash back with this device?

DR. FRIEDE: There is a test. It is relevance may be called into question, but there is a test which achieved 100 percent reduction in splash back.

I bring you back to the statement that was made, everything must be viewed in risk benefit.

CHAIRMAN EDMISTON: It may very well be that a 50 percent reduction gives you the risk benefit ratio that you need. That's the issue that's sort of before us.

DR. FRIEDE: For each different scenario of acceptable risk.

CHAIRMAN EDMISTON: Yes.

DR. FRIEDE: When we've heard it is completely different to be giving little Johnny his measle shot or to be giving the whole population an antiterrorism shot.

CHAIRMAN EDMISTON: So it would seem to me that in your population, the population that the World Health Organization is dealing with, there may be an intrinsically higher risk in some of those subset populations compared to what we see in our own population. Is that correct?

DR. FRIEDE: I would say so.

CHAIRMAN EDMISTON: Therefore, the performance characteristics, because obviously these devices are going to be submitted to the FDA and other nations throughout the world will
be using these devices, the performance characteristics really should be applicable to not just the populations here, but obviously the populations abroad, which will be at a higher risk category?

DR. FRIEDE: Exactly.

CHAIRMAN EDMISTON: Dr. Word?

DR. WORD: I guess I may not necessarily-- I would suggest that we are not here to approve or make recommendations for other countries. I think they have their own licensing organizations. And that we, I think, as a Panel for the FDA, that we should set the standard for what is acceptable for the use in the United States. And then we say this is what we will find acceptable here. If you choose a different scenario outside in another country, then you go to -- you're going to go to their licensing agency. I think that's fair. But I think if we try to break it down for every single -- well, not every single country, but for different regions of the world, I mean you could have a PI that's so long or even just when they submit an application, it'd be so long. Plus, I go back to I don't know if necessarily fair that U.S. reviewers have to do it for the rest of the world and not get compensated for it.

MS. PETERSEN: Perhaps one way to address that issue as well as to look at the issue of risk and relative risk and what's acceptable when is for the FDA to look very seriously at tying the use and restricting use
to specific scenario and saying for this purpose we'll look at this way.

One concern that I have is that we go forward with this because of the issues of injection in other countries and the genuine need in other places to have such a system and our concern about bioterrorism, the device gets approved and then suddenly it's being used in ways where that risk is not really appropriate for the situation. Mass vaccination of school children, for example, or pneumonia vaccine for older people who may already be somewhat immunosuppressed or have other risk factors. Where what we think is, ah, kind of, sort of, usually fairly negligible for most of us is really much more significant of a risk. You know, to tighten those approvals for use in particular scenarios and rule out other uses so that we don't see the drift of risk into places where it's not really appropriate.

CHAIRMAN EDMISTON: You know, in scenarios such as this is very, very difficult to define a relative risk. And I'm really uncomfortable from my own perspective to recommend a percent reduction, not having all the information at hand. I really believe we need to have a more sound epidemiologic model that tells us what the relative risk is going to be for these devices, and then base -- base the performance criteria of new devices coming forward, again, on that risk within those patient populations.

MR. DAVID: Mr. Chairman, I agree with your comment. However, it seems like that
we are presented with technological options that we suggest that we can at least as a benchmark achieve a tremendous reduction into the 90, even 200 percent of the contamination due to splash back. So as a Panel member, I would like to recommend that we will ask the FDA to achieve this type of benchmarking in their consideration of the product.

CHAIRMAN EDMISTON: In terms of that assay, has that assay been repeated by other investigators or is that a single observation from your group?

DR. ZEHRUNG: It has not been repeated. It's only been in-house work at PATH over the last several years.

CHAIRMAN EDMISTON: You know, this really fits more into the assay component. But I think we really need to validate that assay. And I think the FDA needs to validate that assay either from other independent investigators or in-house contractual sources.

But again, relating to the first question, are there any other issues here within this first question that need to be -- yes, sir?

DR. LIN: If you allow me, can I ask PATH presenter a question about --

CHAIRMAN EDMISTON: Yes.

DR. LIN: Do you mind that I ask you question?

DR. ZEHRUNG: No, sir.

DR. LIN: And in your -- I did not have a chance to hear that your product called, but I have a question. The fluorescein dye that you use is water-soluble or is it viscous?
DR. ZEHRUNG: It's water-soluble, yes.

DR. LIN: It's water-soluble. But how much of that would meet actual blood condition, you know the blood is kind of viscous. And did you see any difference, have you --

DR. ZEHRUNG: That's a good question, and it goes to this issue of in vitro and sort of replicating the tissue response. The resulting dye concentration is very viscous, but in terms of comparison to blood, I think that's an interesting point to pursue.

We've focused on the test as a means to induce contamination of the fluid path and using a marker that's actually very inexpensive and very innocuous in terms of safety, and that could be easily detected. But in terms of the protocol and the reports that we put together, we'd be more than willing to share with you.

DR. LIN: Okay. Thank you.

CHAIRMAN EDMISTON: I think in terms of this reduction issue, because my colleagues really brought to my attention that reduction is not a very finite terminology, but one of the other considerations is possibly a significant reduction. A significant reduction in splash back compared to predicated devices. And I think that would address some of the safety aspects of this device.

I want to thank Dr. David for bringing that to my attention.

Yes, Dr. Friede?
DR. FRIEDE: Could I just make a comment on that? Imagine we have two devices out there. And take the example of the device that was presented where we have absolutely no contamination of the fluorescein, not whatsoever. And then we have another device that's called X. And this has a contamination of -- it's significantly better than it was 30 years ago, but we are seeing that 1 out of every 10 shots is getting contaminated, and it is getting contaminated with, let's say, 20 picoliters of what would be liquid. So let's say 20 picoliters of blood.

So would you really consider allowing that device to be used when there is a safer device available?

From my point of view and public health sector, I would be giving recommendations to using the device that has the safer profile, even if it was only safety in terms of theoretical safety.

MR. DAVID: If I can jump in. As a Panel member I'm not convinced that there is 100 percent safe device. This is a short description of a slide that has not been validated. So I would love to believe that this the mainstream rather the extreme, but we don't have data to say this is the benchmark.

So I support your view and I would definitely look at the possibility of looking at 100 percent reduction as the answer to the first scientific engineering question. But I realize that we do not have sufficient data today to ask for that. And by suggesting significant
reduction with a p value that is small, that's getting close to that.

CHAIRMAN EDMISTON: I think there's an underlying issue here that I'm uncomfortable to address, and I'll bring it up again, is that your point is valid. And I think that as the technology improves, we're going to see devices that have a significant impact on reducing splash back. But what the predicated devices, the devices that are already in the field? What can we do about those devices? And I think that's the troubling component. Because as you remember asked Mr. Lin are we talking about guidance for new devices or are we also considering those devices that are currently in the field.

And my question that comes up is that I'm not convinced that these devices are totally unsafe from a cross-contamination perspective. I think that when we look at the relative risk, and that's where I have a problem. If I had really compelling numbers, and I've seen some data that suggests there might be a safety issue. But they're limited studies; animal studies. And also possibly with the application of this new technology, we may be able to get better data on whether or not these devices represent a significant risk for cross-contamination.

It would be difficult for me to say at this time to the FDA, though there are probably people in the audience who would love for us to say this, that these multiple use devices are unsafe and should not be used under
any circumstance. You might be happy for us to say that, too. But I'm just not comfortable personally making that comment or unless my Panel members feel overwhelming that this is the case and these devices aren't unsafe.

DR. BUTCHER: Mr. Chairman, what I would say is that the standard should be set and the preexisting devices should be brought up to that standard for us to say okay.

So I don't see it as a difference. I agree with your point of view. But if we're saying a significant reduction, that means any pre-device should have a significant reduction also.

CHAIRMAN EDMISTON: And it may be entirely possible to retrofit these devices if that's the vendor's wish.

DR. BUTCHER: Yes.

CHAIRMAN EDMISTON: And the vendor wishes not to do that, then these devices may actually go away.

Any other comments? Okay. I think we can move on to question two. Discuss the adequacy and feasibility of the current available methods to assess the potential for cross-contamination and risk of disease transmission by MUNJI devices. And I think we've probably come close to answering that.

DR. ARDUINO: Yes. And basically this is detecting the viral agent in ejectate from a device following its use on a none posit. And you can that now. With the NAT testing and PCR testing that's available, we
could probably do that. And actually figure how many copies.

CHAIRMAN EDMISTON: Any other comments?

Do you think there should be a biological and a physical test in parallel when testing these devices? For instance, the fluorescein would not be a biological test, per se. Would you consider that a biological test or a chemical test, correct? A chemical/physical test?

What does the Panel feel? Does the Panel feel there should be a higher threshold here, not just a single test but at least two tests to validate the ability of these devices to reduce splash back?

MS. PETERSEN: Well, I think if you could do a physical or a chemical type test in a human population, you would certainly be getting a better picture of what actually happens in the clinical setting in the field. And you're looking at the physiological barrier that we're dealing with, human skin as opposed to calf skin, mice which has some different mechanics and physics associated with it.

CHAIRMAN EDMISTON: I understand this a new technology, this assay. Do you feel it'll be possible to correlate this assay with biological assays?

DR. ZEHRUNG: The fluorescein test?

CHAIRMAN EDMISTON: Yes.

DR. ZEHRUNG: I would recommend that it be a combination of a fluorescein or a chemical test, plus a human test with a mark.
And that's why we've focused on hepatitis B and conducting clinical trials as such.

I think that these questions of correlating the in vitro tests to an in vivo sort of model will always be there. And regardless of how thorough you would be in terms of trying to model that, it would just be easier to graduate right to an in vivo model, such as a human being.

CHAIRMAN EDMISTON: Well, there's other models out there for other types of devices in which they look at both bench type data and also like clinical trial type data. So I think that's a valid approach if these devices are going to come forward and we're going to demonstrate their efficacy and safety, then the use of a two or more test to validate their safety and the prevention of cross-contamination is probably warranted.

MS. PETERSEN: I mean, at least in that circumstance you would have a more balanced picture of the risk and you could, I think, more easily consider that risk benefit equation that we keep coming back to from all directions.

CHAIRMAN EDMISTON: Dr. Lin, I think we've been presented data both on the bench and in animal studies and some limited clinical data which suggests that there are assays out there at varying levels of sensitivity. And I would suggest that the choice be made to choose the most sensitive assay to validate the safety of these devices.

Any comment on that from Dr. Layton?
DR. LAYTON: Don't forget, you're going to have multivariant data also relative to the splash back. Just splash back alone without your biological or your human. But your laboratory your bench top is going to give you a tremendous amount of data showing what that is for the level and degree of splash back.

So that's a major part of it also.

CHAIRMAN EDMISTON: From a guidance document perspective in terms of the manufacturer should the FDA then recommend that two or more assays be used to validate the safety of these devices?

DR. LAYTON: I don't have a problem with that.

CHAIRMAN EDMISTON: Dr. Word?

DR. WORD: I don't know should we say one has to in vivo, one because -- I mean you're talking about -- maybe not. You were suggesting like with the fluorescein, that was -- and I don't know if we necessarily have to use fluorescein. They may be able to use something else, just to see if they're getting something back to pick that up, but something that's done in a human. But I think your point was well taken. You want to know if there's actually virus isolated.

DR. ARDUINO: Because if there's no virus isolated and we're not getting virus --

DR. WORD: It's a moot point.

DR. ARDUINO: Then it's a moot point.

CHAIRMAN EDMISTON: Dr. Lin?
DR. LIN: I think the easy road to travel that we have been faced right now as this morning, now FDA has present from our own laboratory, CBER and some people present, although there's some potential-- potentially this is some -- the FDA can recommend to the manufacturer to do some kind of a testing to see whether this splash back or any residual blood remaining after its injection. But the current suggests no any -- that can be directly applied to a MUNJI device. And that is one of the problems we are facing.

I know that Dr. Friede from -- last year he convened a panel of expert to address this issue. I know whether, Dr. Friede, you care to comment to see those methods could be used with it to be applied to a MUNJI device.

DR. FRIEDE: Could you remind me what this assay was I --

DR. LIN: I thought that last year you convened a panel of experts to replace the --

DR. FRIEDE: Yes. The meeting that we had in March last year, we looked at the albumin assay and we decided that this was inappropriate because to actually measure as a surrogate of safety. Because you get albumin and dead skin. And dead skin has no value. You get albumin on the hair.

So at that time we thought that the measurement of hepatitis B as an example of a live virus, which has been suggested here, appeared at the time to be the most appropriate in vivo assay. And my gut feeling is that that
concept of having both in vivo with an in vitro, the in vitro we've been able to get much larger numbers to give you more confidence so that the two together -- but I think there's many ways to do the in vitro as well; enzymes, fluorescein, other things, coloring agents.

DR. LIN: But in your mind, if you don't mind I can ask.

CHAIRMAN EDMISTON: Of course.

DR. LIN: In your mind it is still currently there's any test method that can be applied to the MUNJI device so that FDA want, FDA reviews some of the summation then we say well this is the test you should do to hear that this device is safe for multiple use?

DR. FRIEDE: There is no validated assay yet. I think the assays that we heard about today, if validated when we see the data, I think we'll be able to look at the data and assess whether these are applicable. It looks promising.

DR. LIN: But it's not ready yet --

DR. FRIEDE: The committee did not see all the data last year that we saw today. And all the committee recommended last year was that the evaluation virus was more relevant than evaluating human albumin.

CHAIRMAN EDMISTON: Could Dr. Daya come up to the podium?

Dr. Friede, could you stay there. I just like listening to you.

One of the issues is feasibility. And there will be a burden placed upon the
vendor, the manufacturer if the FDA requires testing.

Let me ask you a question. You described very, very well the technology that you're familiar with that you've had the ability of performing in your laboratory. Does that represent feasible technology from a manufacturing test perspective?

DR. RANAMUKHA: Before that I would like to comment on, this -- I laid out all the methods available. I wasn't aware of the fluorescein method, but the published methods. Out of these published methods the best we can get is 100 copies, 100 genome equivalents per milliliter of blood. With that, you know there comes what is our detection limit we need. We don't know what the limit is. So with that, we cannot say the method in that case. Because that's the lowest we can go down. So that's the question that we are dealing with.

CHAIRMAN EDMISTON: This is a difficult question.

DR. RANAMUKHA: Yes.

CHAIRMAN EDMISTON: Because there's a similar question that comes up with TSE, as you realize.

DR. RANAMUKHA: Yes.

CHAIRMAN EDMISTON: You know, what is the level of infectivity in terms of the prion.

DR. RANAMUKHA: Yes.

CHAIRMAN EDMISTON: And that varies widely. And I think what you described and what's been brought to my attention that I
wasn't aware of is that the infectivity is going to be highly variable depending on where the inoculation is being given.

DR. RANAMUKHA: Absolutely.

CHAIRMAN EDMISTON: So I think that to place an unrealistic burden upon industry to perform at such a high level with probably a very expensive test at this point, it may not be prudent, nor may it be fair unless we have some sound statistical data showing the efficacy of this procedure.

DR. RANAMUKHA: Yes. In that sense, actually, and like I said, there are two methods. One is the HBV-NAT assays and the second is the Taqman assay. Taqman use broader range and also it is feasible because it does not involve a lot of expensive equipment. So it is a feasible assay and then it can be used under diagnostic setting, I would say.

CHAIRMAN EDMISTON: My understanding with the FDA in the past when they've had a situation such as this, they looked at available technology and then the vendor, the industry, the manufacturers have the option to submit data involving one or more of those technologies, correct?

DR. RANAMUKHA: Right. And that's correct.

CHAIRMAN EDMISTON: All right. I think the other issue that comes up, and I think this -- and let me get that fellow that PATH again. You stand up there. All three of you guys stand together, all right. A Kodak moment here.
As a methodology, is that fluorescein a feasible methodology from industry's perspective if it could be used by a variety of vendors?

DR. ZEHURUNG: I would believe so. And it's not only feasible, it's extremely low cost. And the comparison in terms of the assay that's being for the FE testing, it's very expensive. It's $185 a sample to test. So that would actually represent a financial burden to a manufacturer. And we've adopted that or we've accepted that sort of responsibility in terms of our collaboration with the manufacturer. But it's an expensive test.

CHAIRMAN EDMISTON: But I know there's no gold standard. But that probably could be perceived as a possible gold standard if you looked at the rest of the methodologies out there.

I think the fluorescein assay has great promise, but the concern I have is that I've only seen the data presented from your institution. And we'd need to see more data with a variety of devices.

So I suspect what I would consider to present to the panel is that we have methodology available that the FDA could require the vendor to submit performance data using a number of those current methodologies. If the fluorescein assay appears a successful assay, then I would also encourage the FDA to consider that as one of the surrogate tests. But I think at this time I'm not sure if we could recommend that assay because we don't have the kind of
laboratory experience with that as we do with the other methodologies.

Any comments from the Panel on this? You guys agree or disagree or --

MR. DAVID: I agree, yes.

CHAIRMAN EDMISTON: Okay. So I believe in terms of question two, the methodology that should be applied should be feasible and should be adequate. And we currently have presented published methodologies which are accepted by the scientific community to detect biological particles in samples, both blood and other body fluids. Is that a reasonable consideration.

DR. LIN: I wanted to ask PATH, is your method is going to be published in an open literature?

DR. ZEHRUNG: That's a good question. We've discussed that and I think we've just focused on supporting any sort of regulatory submission for the data. But I think we would be open to doing that.

CHAIRMAN EDMISTON: Would you accept their data from a regulatory perspective if it's not peer reviewed methodology?

DR. LIN: Well, as long as it's scientifically sound, then we don't have a problem whether it's published or not.

CHAIRMAN EDMISTON: Okay.

DR. LIN: But my question is that to be aware to other manufacturing, if the method is published, and then somebody could use their method to compare --
CHAIRMAN EDMISTON: Is this a proprietary methodology?

DR. ZEHRUNG: No. I mean, we haven't designed any sort of patent, you know, applications for it. So I think our position would be it would be free to industry to use.

CHAIRMAN EDMISTON: So you don't consider it proprietary? Does that fellow back there consider it proprietary or --

DR. ZEHRUNG: From Felton? No.

CHAIRMAN EDMISTON: The gentleman who was with you?

DR. ZEHRUNG: Dr. Loskutov?

DR. LOSKUTOV: No.

CHAIRMAN EDMISTON: No? Well, I think it would be in the best interest of the industry as a whole if we had that data available to us in a published form.

DR. ZEHRUNG: And as I said earlier, PATH is more than willing to collaborate and share this information with these technologies.

CHAIRMAN EDMISTON: Are there any other comments on question two?

MS. PETERSEN: Has PATH made any effort to seek some kind of grant or collaborative funding to assist with the higher cost of some of these assays to get the validation?

DR. ZEHRUNG: Well, that's part of the funding from the Bill and Melinda Gates Foundation is to conduct the safety testing for the protector cap injector. And so that would be --
CHAIRMAN EDMISTON: Dr. Friede, do you have any final comment on this issue here?

DR. FRIEDE: No. As I said, this is the best we've seen.

CHAIRMAN EDMISTON: Excuse me. You pronounce your Friede?

DR. FRIEDE: Friede.

CHAIRMAN EDMISTON: Friede?

DR. FRIEDE: Yes.

CHAIRMAN EDMISTON: All right. I had that totally screwed up, didn't I.

DR. FRIEDE: I think that from what I -- my personal view is that this has set for the moment a benchmark. This is the most sensitive we've seen. It is a 100 fold more sensitive than anything else we've seen. And I think from my perspective we're going to try to go for as safe as possible.

CHAIRMAN EDMISTON: We're talking about the fluorescein assay?

DR. FRIEDE: The fluorescein assay.

CHAIRMAN EDMISTON: But as a scientist also you would want to see that be submitted for peer review?

DR. FRIEDE: I would want to see it permitted for peer review. I would also somewhere along the line like to see somebody try and if possible, look at this and say how does this correlate with real life situation. Because we are talking about an in vitro situation. And so if this is possible somewhere the line. But I do like the fact that it can probably be repeated in many laboratories,
easily done and we can probably even have these kinds of things standardized.

CHAIRMAN EDMISTON: And I think that's an excellent point, but I'm not sure that's the purview of the FDA. I mean, that's something that's going to probably conducted independently, or at least within their laboratories if they have an interest in this.

Any other questions in terms of -- any comments?

DR. LIN: I tell, you would echo Dr. Friede --

CHAIRMAN EDMISTON: Friede.

DR. LIN: His comment. Can correlate those and test results with their ongoing current study. That will be wonderful. It will be an excellent correlation for that. So data can be compared.

CHAIRMAN EDMISTON: Any further comments on question two?

Did you understand our response in question two, that there currently are feasible and adequate assays available which the manufacturers could use to benchmark their device.

DR. LIN: Okay.

CHAIRMAN EDMISTON: Number three, Feinman, et.al. suggested a volume of blood as small as 10 picoliters can transmit hepatitis B virus in chimpanzees. However, this finding is based on a single animal study. Considering the potential public health benefit of MUNJIs is there a threshold volume of blood contamination that presents an acceptable risk? If so, what
threshold would be considered acceptable? Any comments by the Panel?

DR. ARDUINO: I think we're focused on the wrong thing because it all depends on what the viral load is on the person -- you know. I mean, this is a single animal. I mean, it's not a population. I mean, we have no idea what real infectious dose is based on what, an N of what? And it's kind of out of context. Because this wasn't in vaccine development. This was more looking at a test development for detection of virus.

So, you know, I'm kind of -- you know, 10 picoliters, how we going to measure 10 picoliters? It's also based our serum albumin studies which is probably a lousy test to begin with. So, you know, how accurate is that really when you look at the other assays they're using to measure that?

I would still look at reduction of the infectious agent or you can demonstrate that there's no infectious agent or to whatever the limit of detection of the tests are.

CHAIRMAN EDMISTON: From biological perspective?

DR. ARDUINO: From a biological perspective.

CHAIRMAN EDMISTON: How about the concept of a genome equivalent?

DR. ARDUINO: Well --

CHAIRMAN EDMISTON: That's the same thing?

DR. ARDUINO: That's a copy.

CHAIRMAN EDMISTON: Okay.
DR. WORD: I'm sorry.

CHAIRMAN EDMISTON: Dr. Word?

DR. WORD: I would probably go with the lowest level detectable. Because generally if it's not detectable, we say it's negative if you're looking at copies of something.

I'm not comfortable with that 10 picoliters at all.

DR. ARDUINO: And we're using hepatitis B as a marker, you know it's great -- transmission requires -- it's great -- you know, has more potential transmission than the other viruses.

CHAIRMAN EDMISTON: Dr. David, any comment?

MR. DAVID: I thought I have an idea until I heard the comments. Now I'm not concerned. It sounds to me like you're saying 10 picoliter is a number you're not comfortable for several reasons loading N on one --

DR. ARDUINO: It's all based back on the virus. You know, you really don't know what the -- and the viral load depending on, you know, whether you're HBV, HIV infected, HBV and HCV infected or HBV alone, or HBV with e antigen. It's going to be different.

So I would rather focus on, you know, the lowest detectable amounts of virus.

CHAIRMAN EDMISTON: Dr. Word?

DR. WORD: I guess my other question is do we have to include other viruses that we've known are blood born, not just -- I mean, I know hepatitis B is the most easily transmitted. But just like when we screen for
blood, we screen across the board for hepatitis A, B and C and we'll also look at HIV. Do we have to set a limit for all of those, not just hepatitis B? I think I'd feel more comfortable, because why not treat it the same way if you're telling me there may be some back splash in their blood there. I don't know how other people feel about it, though.

CHAIRMAN EDMISTON: Well, we've been shown methodologies that exist that detect anywhere from one to 0.4 picoliters of fluid contamination. You don't feel that going down to the -- one to 0.4 picoliters would be a sufficient threshold?

DR. ARDUINO: No, it's hard.

CHAIRMAN EDMISTON: Dr. Layton?

DR. LAYTON: Well, I think from an industry perspective you want to try and put a limit on it. And it goes back and relates there to the question one also. Now whether it's 10 picoliters or what is it, 0.4 or .4 picoliters. And we're looking at total reduction of splash back. And you put a limit on it today, you don't know, you know next year we may have another blood born disease that plays an issue relative to it. So that's why the best from an industry standpoint and from my recommendation, you try to put a limit on it relative to a volume.

CHAIRMAN EDMISTON: What is the FDA's perspective on threshold.

DR. LIN: Well, that's the question that we try to ask of our panels to help us. You look at this morning's presentation, this is
potential public health need that somebody probably already present. And whether I say in this country or in other country or in other third world country, this is a potential public health need. On the other hand, this also has potential risk of blood cross-contaminations.

Now if from looking at the risk benefits consideration, our question to you is that in your mind we should not allow any risk or threats of risk or we should allow for certain level of risk. That's the question that if you can help to address that, it would be very helpful.

CHAIRMAN EDMISTON: Well, what you're saying is that we get back to that 100 percent issue of reduction in splash back?

DR. LIN: Right. Right. Yes.

CHAIRMAN EDMISTON: And I think if that's the case, then we can take it one step further, that's no detectable viral particle or detectable blood --

DR. ARDUINO: Except we really don't have, other the fluorescein, which is a surrogate, we really have no way of actually measuring that level of blood.

DR. LIN: I think that that's why you have to look at question number two, which is also the current available method.

CHAIRMAN EDMISTON: Right.

DR. LIN: Is there any way you can really direct to the level. And if not, then what kind of level you can recommend to FDA that would be appropriate for the reviews of this type of device.
CHAIRMAN EDMISTON: Well, if you review the published assays, especially HBV assays, hepatitis B virus assays, you're limit of detection varies anywhere from .1 nanograms to 10 to the 9th, depending again on the methodology. And if you go 10 to the 9th, we're talking about a threshold that we initially discussed early on, anywhere between 1 and 10 picoliters, correct?

So we really need some consensus here in terms of what the Panel believes to be a threshold value. And I think Dr. Friede suggested that 10 picoliters was much too high, correct?

DR. FRIEDE: I think just looking at the numbers, we know that 10 picoliters can transmit infection and less than 10 picoliters will therefore be able to on some occasions.

CHAIRMAN EDMISTON: So on a risk benefit basis more than likely what we're talking about is a device that has the capability of reducing -- reducing exposure to below 10 microliters -- 10 picoliters? Correct?

DR. WORD: Excuse me, Dr. Edmiston. What is the acceptable level that we use in blood when we transfuse someone? I mean, I don't know what the exact number is. I don't know if anyone here might know?

CHAIRMAN EDMISTON: Dr. Michaud?

DR. LIN: She's a hematologist, so she'll be --

DR. MICHAUD: Ginette Michaud, Deputy Director of DAGID.
I would suggest in fact the question may not be entirely relevant to this discussion. Because I believe that the acceptable limits are driven by the available technologies. And the tests are applied to blood products which are lifesaving biological products. So it's really, I think it's a very different thought process that goes into that.

And as you look at the history of screening of blood products, the limit of detection on the acceptable assays has been driven down as the technology is able to offer a lower limit of detection.

CHAIRMAN EDMISTON: So we're actually back to the risk benefit component again in the sense that the technologies that we have in front of us here have variable specificities or variable units of detection. And I think that Dr. Friede's comment is that if we're going to try and achieve maximum reduction, maximum risk with overall benefit of the device, then we need to look at that value less than 10 picoliters. Would you agree with that?

DR. BUTCHER: Mr. Chairman, I don't think that we're going to be able to put a number on it, but I think that going to your previous thing that significantly reduce it down and that would get it. I mean, we know that the ten is too high. We don't have enough evidence with those that are less yet.

CHAIRMAN EDMISTON: Yes, sir?

MR. WATSON: I'd like to put a little perspective on the numbers. I know that
it's a little bit of a challenge to actually pin it down.

When we look at substantial equivalents, which right now what we're actually proposing to do is set an actually kind of a bar, which is a little bit of a challenge in the 510(k) process, but it can be done when we have safety concerns. If we can get a number -- realizing that that is a challenge, if we can get some kind of a bar to start with. Because we can always make that bar higher as we know more about the developing technologies.

Right now we don't -- I mean 10 picoliters has come up or 10 picoliters has come up and we don't really know what to do with that.

CHAIRMAN EDMISTON: Right.

MR. WATSON: As you mentioned, you know, less than 10 picoliters, at least if the Panel -- and I'm not suggesting that they should -- but if the Panel would give us that as a starting point, that would help us tremendously. But other than that, it's sort of a touchy situation for us because then we don't have a goal in place without that.

So I would encourage any valuable numbers that you think based on what you've seen today, if you can give us some guidance in that area, that would be much appreciated.

CHAIRMAN EDMISTON: The NAT technology, can the NAT technology detect down to 10 picoliters? NAT? I'm not sure it can.

DR. RANAMUKHA: NAT technology detected DNA copy numbers. So it does not go
with the volume. And so it comes down to how many copies you find in the --

CHAIRMAN EDMISTON: Getcha. Getcha.

DR. ARDUINO: That's why I almost saying that ten is irrelevant if you're looking at how many genomic equivalence are present.

DR. WORD: I was going to say I like presence --

CHAIRMAN EDMISTON: Well, the issue is is that copies or genomic equivalents is a nice ideal number. But the issue is also in terms of volume of detection. And I'm a bit perplexed by this number issue, you know.

MR. DAVID: And the number is what I'm left today after seeing the data, is that 10 picoliter is transmittable volume and would give a significant concern if we are supposed to judge risk to benefit as the safety issue is not addressed.

So definitely I'm looking for a volume that is below that numbers, because then I showing this number is unsafe.

CHAIRMAN EDMISTON: And realizing, too, that number, 10 picoliters, was based on a single study, correct? A single study.

DR. ARDUINO: In one animal.

CHAIRMAN EDMISTON: In one animal.

But it does represent a starting point.

Does the Committee have any concerns with making a recommendation of less than 10 picoliters as a bar?

DR. ARDUINO: As a start.

CHAIRMAN EDMISTON: Start.

DR. ARDUINO: No.
DR. WORD: Can you put the caveat that they will revisit it?
CHAIRMAN EDMISTON: Oh, they'll revisit it, there's no doubt about that.
DR. WORD: No. But if you tell them.
CHAIRMAN EDMISTON: This is a moving target. Am I correct in understanding that this is a moving target, correct?
DR. LIN: Well, when you set the benchmark, then I'm sure that industry can -- but once you set the benchmark, the industry would develop a tendency to meet that goal. Hopefully.
CHAIRMAN EDMISTON: You represent sort of the pragmatic perspective here, Dr. Friede. You're out there in the field. If industry met that benchmark of less than 10 picoliters, would that give you a sense of assurance that we're moving in the right direction, especially if we evaluate the risk versus benefit component.
DR. FRIEDE: Okay. Let's just imagine the situation. We have a device, again this famous device X, and it's actually transmitting 5 picoliters per injection. That's less than 10. And we know that we're in a room with 50 percent chronic carriers, and they're all looking very yellow. And we all have to stand up and we have to inject the person standing next to us and then inject ourselves. How many people here are going to do that, especially if there was another device that was
undetectable using the most sensitive assay, absolutely undetectable?

So for me putting a number and saying five or less than ten, this is not relevant. It must be undetectable using the most sensitive assays that we have. Because if you can detect blood on it, then there is a risk. That risk might be, as Dr. Kane mentioned, you know I presented the worst case scenario and we should also be looking at the best case scenario. But we are going to have a recommendation to people to use a device. And if we know that that device, we say oh yes, use it, it does transmit blood but not a lot. Don't worry about it. I'm not comfortable with that. I think we have to say there is no detectable --

CHAIRMAN EDMISTON: So in essence we would raise the bar to a level we don't even raise with TSE?

DR. FRIEDE: Yes. I don't know what you do for TSE, but it does appear to me that we have seen this morning data which suggests that there is something that does not have any transmission. It appears to me that this is a benchmark and one could not allow anything which is worse than that.

CHAIRMAN EDMISTON: What's the Committee's perspective on Dr. Friede's comment that no detectable -- let me get a vote here. How many feel that the Committee's recommendation for this question should be that there is no detectable entity?

Everyone who feels there should be no detectable entity. One, two, three, four.
Four to two or four to three. So it would appear that the Panel would recommend that there would be no detectable entity.

I think that that's a very difficult thing to achieve, but that's the Panel's recommendation.

Any comments from the FDA in terms of that recommendation?

DR. LIN: Well, we can live with.

CHAIRMAN EDMISTON: You can deal with it?

DR. LIN: We can, yes.

CHAIRMAN EDMISTON: Okay.

All right. What we're going to do at this time is take a brief break or do you want to continue on. Well, I'll tell you what, let's have a very quick break. Let's have a five to ten minute break and we'll come back, and at that time we'll finish up with a final public comments.

(Whereupon, at 2:17 p.m. a recess until 2:29 p.m.)

CHAIRMAN EDMISTON: I'd like to call this meeting back to order. We will now hold our second half hour open public hearing. If there any individuals wishing to address the Panel, please raise your hand, identify yourself at the time. Also at the time you identify yourself, please indicate again any proprietary interests or conflicts of interest. Please.

DR. KANE: Yes, my name is Mark Kane. I work for PATH. I spoke before and I have the same conflict of interest profile as the other PATH speaker.
I think the point I'd like to make is that is a perspective that comes from a little bit of the history of the development of some of these assays.

The original intent in developing the serum albumin assay, at least at a certain point, was that we would in parallel develop a physical chemical test like the serum albumin assay in parallel with a biological test looking at the actual etiologic agent that we were most concerned about, which is hepatitis B. Then because although the hepatitis B testing is sensitive, specific and available, it is not an easy task for a manufacturer to go out and go to China and get 300 hepatitis B carriers and undertake the kind of study that is being proposed by PATH.

So the idea was to use the hepatitis B testing as sort of a gold standard, correlate that with the physical chemical test like serum albumin. And in the future it would be possible for manufacturers just to use the simpler test.

Now, that did not work out because the serum albumin test was not acceptable because of contamination from the environment, because we live in a sea of the stuff. But the principle that you have a biological assay available that measures exactly what you're worried about, the highest titer pathogen hepatitis B and the major pathogen, you're actually lucky to have that available to you. But if that could be correlated with an assay, a much simpler assay like the fluorescein in the future, then it might be possible at a certain
point when all the tests have been validated, to move over to a much simpler and cheaper test. But conceptually I would think the gold standard would actually be the hepatitis B model, because you're measuring exactly what you're worried about.

And the second point I'd like to make is that I totally agree with the Panel's recommendation that they should basically accept zero detectable level of contamination. My concern is that that doesn't go quite far enough to answer all the questions that need to be answered. Because there exist out there a number of detection systems with different outputs and with different levels of sensitivity and specificity.

So, for example, the fluorescein test which the panel seemed to be interested in gives you a readout in terms of volume. Some of the DNA tests for the hepatitis B virus give you an output in terms of genome copies. All of these can potentially be useful. So some kind of guidance, I would imagine Dr. Lin, you know which one of those might be -- some direction, some guidance to the FDA might be very helpful to them.

For example, there's been a history of different levels of sensitivity and specificity. In the '60s it was visible blood. Then it was a blood dip stick. Then it was an ELISA test of the sensitivity and specificity of blood ELISAs. Then it was PCR, and now it's fluorescein. And certainly it's a moving target. But basically if someone said well there
was no visible blood on the head, would that be acceptable? No. Would a dip stick be acceptable? Probably no. Would the fluorescein and PCRB and the best we have for those two lines be acceptable? It's the best we can do right now.

So, you know, some sort of guidance along those lines I would guess might be helpful as well to the FDA.

Thank you very much.

CHAIRMAN EDMISTON: Does the panel have any questions for the speaker? Yes, Dr. Word?

DR. WORD: I don't have a question. But when he started talking about the hepatitis B and how many copies, I think if you're looking for FDA for the guidance, you're looking at license test that your agency itself has licensed. And if you get down to the lower limit of detectable, whether it's 200 copies or 150 copies, if it's 200 copies then it comes in at 199, then but it's nondetectable.

But I guess what I'm saying is when he was suggesting that you have to use a test because there's so many, you know which ones you've licensed. So I don't know, do we say it has to be one that's licensed in the United States because that's the only one you're going to look at?

DR. LIN: You're asking me to comment? Well, the one that licensed, from our sister center, Center for Biologics and CBER, these centers their licensing for blood donation, blood donor. But here the one that
we're talking about to assay the procedure biocopy; that you don't have to use that kind of blood licensing because that's totally different method.

But here I think that probably one of the challenges is how you assay those virus remain on those top or any fluid pathway. That is probably most of the challenge that the manufacturer is facing. How you excerpt those virus out to assay for those copying.

CHAIRMAN EDMISTON: Dr. David?

MR. DAVID: Thank you, Mr. Chairman. Just to clarify in my mind what the Panel voted on is a question to the FDA is the capability that you have if you have -- you kept asking would should FDA do if they have an application submitted tomorrow. And in this kind of time frame is the FDA capable of reproducing tests to a level that the Panel has recommended?

DR. LIN: I shouldn't have used the term "tomorrow." I don't mean right away. I mean just in the near future we get a submission. But the Panel's recommendation that will help us to prepare a guidance document to the industry. That's essentially what I mean.

MR. DAVID: Okay.

CHAIRMAN EDMISTON: Do we have any further speakers from the public?

Dr. Zehrung, could I call you to the podium for a moment?

DR. ZEHRUNG: Yes.

CHAIRMAN EDMISTON: This is more from a reviewer perspective, all right. This
device that you have that fits on the end of your injector?

   DR. ZEHRRUNG: Yes.

   CHAIRMAN EDMISTON: The splash back that may occur is contained within the bottom chamber, is that correct? Is this positioned the right way on the device with the --

   DR. ZEHRRUNG: Yes, sir. The flat portion is the skin side.

   CHAIRMAN EDMISTON: The flat portion is the skin side.

   DR. ZEHRRUNG: So that outer flange would then contact the skin.

   CHAIRMAN EDMISTON: Yes.

   DR. ZEHRRUNG: And then the tail end of it, actually, comes into close proximity to the nozzle of the --

   CHAIRMAN EDMISTON: Okay. This part right here. Okay.

   DR. ZEHRRUNG: Yes.

   CHAIRMAN EDMISTON: Like that?

   DR. ZEHRRUNG: Right.

   CHAIRMAN EDMISTON: Like a flying saucer, correct? Okay. And so any potential splash back is contained within this bottom chamber, is that correct?

   DR. ZEHRRUNG: Both chambers.

   CHAIRMAN EDMISTON: Both chambers?

   DR. ZEHRRUNG: Yes.

   CHAIRMAN EDMISTON: So let me ask you a question. It's contained in both chambers. Is there a membrane that is above this?

   DR. ZEHRRUNG: There is membrane.
CHAIRMAN EDMISTON: There's a membrane?

DR. ZEHRUNG: That's --right. So on the side that's in close proximity to the nozzle --

CHAIRMAN EDMISTON: Yes.

DR. ZEHRUNG: -- there is a thin polyethylene film that the injection stream pierces on its way through the protector cap and then into the tissue.

CHAIRMAN EDMISTON: Is that also a replaceable membrane or is that a permanent membrane?

DR. ZEHRUNG: It's permanent. It's actually welded onto the backside of the protector cap during the fabrication process.

CHAIRMAN EDMISTON: Okay. And that membrane prevents the splash back from getting back into the nozzle component of the device?

DR. ZEHRUNG: So far studies have indicated that that's the case.

CHAIRMAN EDMISTON: Okay. And basically what you've seen to date is there is no -- when you remove this membrane and you look at the -- there obviously is some residual material on the membrane in the top, correct?

DR. ZEHRUNG: Sometimes.

CHAIRMAN EDMISTON: Sometimes.

DR. ZEHRUNG: Especially with the fluorescein test which is an exaggerated sort of test.

CHAIRMAN EDMISTON: Okay. But it greatly reduces to a significant extent --

DR. ZEHRUNG: Definitely.
CHAIRMAN EDMISTON: -- the infiltration of that splash back into the nozzles?

DR. ZEHRUNG: That's true.

CHAIRMAN EDMISTON: Does that answer questions out there? Okay. Very good. Thank you so much.

Do we have any further comments or questions?

At this time, I believe I have to turn it over to my Executive Secretary to read a statement.

EXECUTIVE SECRETARY COLBURN: Well, before we adjourn for the day, I just want to remind the Panel members that all the material that you have received for preparation and review for this Panel is not considered proprietary, and you do not need to destroy this as if it was a PMA panel or something like that. So you are free to keep the material that you have received.

And I just want to extend my thanks and gratitude for all the Panel members, and invited consultants from other panels who have helped us out in conveying for today. And we appreciate all your very informative comments.

And I would also like to extend my thanks to Dr. Friede from WHO coming and presenting to the Panel, as well as the industry representatives that have helped us out in guiding the discussions today and helping us come to at least a consensus and direction where we can forward in developing of these devices.

Thank you.
I'll return this back to Dr. Edmiston for any final comments.

CHAIRMAN EDMISTON: And I also want to express my sincere thanks to the members of this Panel for this diligence and interest and effort in today's activities. And the members of the public, especially Mr. Hooks for his presentation. And also the members of industry for really a very interesting presenting of what could be some new emerging technology.

If there is no further business, I would like to adjourn this meeting of the General Hospital and Personal Use Device Panel. Thank you very much.

(Whereupon, the meeting was adjourned at 2:41 p.m.)