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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**MICROBIOLOGY DEVICES PANEL MEETING**  
**MEDICAL ADVISORY COMMITTEE MEETING**  
**OPEN MEETING**

Thursday, February 12, 1998

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P R O C E E D I N G S

DR. THRUPP: To start with, Freddie Poole, our executive secretary, has some comments.

**Opening Remarks**

MS. POOLE: Good morning and welcome to our Microbiology Devices Panel. I have some housekeeping announcements first.

The panel were given some direct deposit forms. You have to fill them out today and leave them with me before you leave. Thank you.

We also have a conflict of interest statement to read.

The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the

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potential conflict of interest involved, is in the best interest of the government.

Waivers have been granted to Drs. Ada DeForest and Valerie Ng for their financial interests in firms at issue which could potentially be affected by the committee's deliberation. The waiver permits these individuals to participate in all matters before the committee.

Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Jay Hoofnagle, Paul Edelstein, Valerie Ng, and Lauri Thrupp.

Dr. Hoofnagle reported that firms at issue provide his laboratory with reagents to evaluate assays for hepatitis and he has written papers on these assays. In the absence of any personal or imputed financial interest, the agency has determined that he may participate in the committee's discussion.

Drs. Edelstein and Ng reported potential contracts with firms at issue. Dr. Thrupp reported that a firm at issue donated money to his institution for education and research purposes. Since these involvements are not related

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to the specific matters before the panel, the agency has determined that Drs. Edelstein, Ng, and Thrupp may participate in today's discussion.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him- or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

One other housekeeping. The panel has a lunch sheet. If you want to eat lunch here in the building, could you fill that out and someone will collect it with your \$5.25 for the lunch.

Thank you.

DR. THRUPP: Thank you, Freddie.

I wasn't able to find any typographical error in the agenda for today like our sexually transmitted devices agenda item from yesterday, but with the breadth and depth of the questions that Dr. Ticehurst has produced for us, we may be all ready to have our own livers tickled by some

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libations by the end of today.

To begin with, we want to introduce the panel members. Let's start on the opposite side. Dr. Hollinger, would you introduce yourself and give your affiliations.

DR. HOLLINGER: Blaine Hollinger, Baylor College of Medicine, Houston, Texas.

DR. TUAZON: Carmelita Tuazon from George Washington University Medical Center.

DR. HOOFNAGLE: I am Jay Hoofnagle from the Division of Digestive Diseases and Nutrition of the National Institutes of Health.

DR. STEWART: John Stewart from the Division of Viral Diseases, Centers for Disease Control and Prevention.

DR. NG: Valerie Ng, University of California, San Francisco.

DR. EDELSTEIN: Paul Edelstein, University of Pennsylvania Medical Center.

DR. ZABRANSKY: Ron Zabransky, VA Medical Center in Cleveland, part of the Ohio VA system.

MR. RODRIQUEZ: Luis Rodriguez from San Antonio College. I am the consumer representative.

DR. GATES: David Gates with Becton Dickenson. I am the industrial rep.

DR. GUTMAN: Steve Gutman. I am the Director of

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the Division of Clinical Laboratory Devices.

DR. DeFOREST: I am Ada DeForest, Allegheny University of the Health Sciences and St. Christopher's Hospital for Children.

DR. KADREE: Margaret Kadree, Morehouse School of Medicine.

DR. SPECTER: Steven Specter, University of South Florida College of Medicine, Tampa, Florida.

DR. CHARACHE: Patricia Charache, Johns Hopkins University School of Medicine.

DR. THRUPP: Lauri Thrupp, University of California, Irvine.

Let's move right in to program with introducing Dr. Gutman to give us an overview.

#### **Opening Statement**

DR. GUTMAN: Good morning. The objective of the panel meeting today is to begin a process of defining guidance for the Division of Clinical Laboratory Devices and for Industry for characterizing performance of tests of the diagnosis and monitoring of viral hepatitis.

Viral hepatitis is now recognized to be caused by at least five viruses which cause a somewhat dazzling array of disease states. Although, since 1966, more than 28,000 reports on these diseases have appeared in the medical

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literature, there is much to learn about both these pathogens and the diseases they produce.

We view today as a starting point to generate dialogue with members of our panel, medical professionals and members of industry on scientific criteria to be applied to the review of hepatitis in vitro diagnostic and monitoring tests.

We recognize that this is a large and difficult task and that there are many nuances involved in hepatitis testing. While it would be unrealistic to believe we can address all the issues and define all the answers at this one point in time, we hope to gather information of value to both the agency and the manufacturers on the acceptable scientific evidence needed to bring new hepatitis devices to market.

FDA develops guidance documents as a mechanism for communicating review recommendations and considerations to sponsor. Our guidance documents also assist us in standardizing our approach for premarket review.

FDA has implemented good guidance practices, so-called GGPs, agencywide enabling us to develop more valuable and consistent guidances. We are strongly committed to following these practices in developing guidance in the Division of Clinical Laboratory Devices.

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Today's discussions will be an important initial step in developing guidance for these products with public input and in conformance with the GGPs.

FDA guidance is not binding. Instead, our guidance is intended to provide insights into possible ways to address scientific concerns of importance to the agency with regard to a test or a set of tests.

Sponsors may choose to follow FDA guidance literally or to propose alternative pathways for answering the scientific concerns expressed in FDA guidance. With the implementation of the good guidance practices, we have established a mechanism for formally seeking input during the develop of guidances.

This mechanism includes internal review of the draft guidance across offices and other centers where appropriate, followed by a public comment period on the draft. The GGPs oblige FDA to consider all comments received and provide us the option of revising the guidance before its implementation as a final working draft.

As some of you may be aware, while the Division of Clinical Laboratory Devices in the Office of Device Evaluation has always been the lead group for hepatitis A, IgM anti-hepatitis-B core and hepatitis e-antigen and its antibody, until last year, all blood-bank screening and

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other diagnostic test for hepatitis B and C were reviewed in the Center for Biologics.

During the past year, an administrative change has been made for the Center for Biologics to continue to take responsibility for reviewing hepatitis products intended for blood and blood products safety, while our center, the Center for Devices, has been assigned to take responsibility for reviewing these products for non-blood bank diagnostic or monitoring purposes.

Obviously, it is important to both centers to have appropriate scientific and administrative consistency among our review processes. The program for today will provide an overview of device review in the Centers for Devices and the Centers for Biologics and then will address a series of both general and specific issues of interest to the agency, but particularly of interest to our division.

The Division of Clinical Laboratory Devices has had opportunities to interact with a number of sponsors who plan to market one or more tests for hepatitis for a variety of diagnostic purposes. Preliminary review of one study protocol resulted in a review summary which has been shared with a number of members of industry.

This document was not considered to be actual guidance, but was an informal effort by the division to

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address scientific issues relating to the development of tests for hepatitis B virus. It is our hope that today's deliberations will serve as a base for actual guidance documents to be developed following good guidance practices.

Today's deliberations will be focused on the three viruses which are most relevant to the Division of Clinical Laboratory Devices: hepatitis viruses A, B, and C. You will get your money's worth today.

While hepatitis A and B are relatively well understood, hepatitis C is relatively new and the subject of ongoing intense inquiry. The diagnosis of all of these viruses have in common the challenge that there are no laboratory or clinical gold standards against which they can be easily characterized.

There are two important themes of considerable current importance at FDA as a result of legislation passed last year. The first is the need for the agency to interact in a more proactive, intense and upfront manner to help sponsors develop good studies that would support rapid review and entry of devices into the marketplace.

The second is the need for helping companies identify, to quote the law, "the least burdensome appropriate means of evaluating device effectiveness." Translating that directive into policy means that we are

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charged with asking appropriate questions to determine performance is safe and effective, but attempting to avoid questions that might be academically quite interesting, but go beyond the threshold of providing insight into basic safety and effectiveness. Identifying the right questions and appropriate minimum data sets are ongoing challenges to us and are the key reasons for convening the panel, this panel, to request input.

One interesting and important option review for PMAs, which has always been the ability to require some data sets be generated in studies following preliminary pre-market approval, the new law adds emphasis to this point by stating, "In making a demonstration of a reasonable assurance of the effectiveness of a device, FDA shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls."

I challenge the panel today as they consider FDA's list of questions to keep this new directive in mind.

Since we view today's deliberations as a starting point, we would encourage members of the panel and of the public to consider the questions raised today as an opportunity for further comment. We will be actively

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soliciting input for 90 days following this meeting to help frame our thoughts on how to move forward with a more finely tuned series of guidance documents.

FDA approaches to evaluating Class III assays have been at times somewhat different at the Center for Devices and the Center for Biologics because of different indications for use of these assays.

We will now have short presentations from Tom Simms from the Center of Devices and from Leonard Wilson from the Center of Biologics to explain each center's approach and the historical perspectives that yielded these approaches. It is hoped that these presentations will provide background for discussion about appropriate studies as our center assumes a greater role for diagnostic and monitoring indications.

Tom.

### **FDA Presentation**

#### **Background and CDRH Regulatory History**

MR. SIMMS: Good morning. My name is Tom Simms and I am a reviewer in the Microbiology Branch. What I would like to do today is try to offer definitions for terms you will be hearing today.

[Slide.]

These definitions are based on our regulations,

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policies, and the law, and perhaps I may offer some insight on why we ask for the studies or certain studies that we do. How does the FDA determine what the applicant is claiming their assay will do?

This determination is made from the assay's intended use and indications for use statement. Examples of intended use and indications for use for hepatitis assays will be discussed by other FDA presenters.

For the FDA, intended use and indications for use have the same meanings and indications, but it has been interpreted that there are two meanings, such as intended use defines the detected analyte. For us analyte is what the assay will detect, such as antibodies to hepatitis B core antigen.

Indications for use has been defined as the disease or infection which is being diagnosed and what group of patients.

[Slide.]

Our definitions for intended use and indications for use are the intended use is the objective intent of the persons legally responsible for labeling of the devices. The intent is determined by the person's expression or circumstances surrounding the distribution of the article.

[Slide.]

The indications for use identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device, as labeled, will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device.

[Slide.]

The definition further states that when indicated or intended for use in selected subgroups of a population with a disease symptom or syndrome, the labeling should identify specific tests needed for the selection or monitoring of the patients and, if relevant, include information regarding the recommended intervals between device use, the usual duration of treatment, or any modifications of such.

According to FDA law, all Class III devices must be shown to be safe and effective for their intended uses.

[Slide.]

To be shown safe and effective, a device must be demonstrated to be safe when, based on valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

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[Slide.]

A device is effective when based on valid scientific evidence that with a significant portion of the target population, the use of the device for its intended uses and conditions of use when accompanied by adequate directions for use and warnings against unsafe use will provide clinically significant results.

[Slide.]

How is information collected to support claimed indications for use? The following slide should be familiar to everyone present. Well-controlled studies are required, and well-controlled studies have a study plan or protocol that has a clear statement of the objectives, a method for the selection of the study subjects to avoid outcome bias, an explanation of the methods of observation and recording of results, a comparison of the results of diagnosis with a control in such a fashion to permit quantitative evaluation. Plus we also have one other option for the collection of data.

[Slide.]

The Commissioner of FDA may rely on other valid scientific evidence from which there is sufficient evidence to determine the device's safety and effectiveness. This is used when it is determined that the requirement of

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well-controlled studies are not reasonably applicable to the device.

Clinical studies may also involve the comparison of the new device's results to results obtained from another commercial assay or reference assays. Reference assays are assays that have been well established and have a very defined diagnostic interpretation associated with them, such as complement fixation testing performed using a CDC-recommended procedure, electron microscopy, or viral neutralization.

Assay to assay comparison may be inappropriate since all assays are not created equal. This means even though assays may be constructed with the same antigen or capture antibody, due to design differences, they may have significant differences in performance characteristics.

Another option that we would have would be in-house or CDRH in-house testing of assays. This option is not currently available to us. CDRH makes its decision on the safety and effectiveness of an assay by a review of applicant's submitted information.

This is entirely a paper review similar to that performed prior to published peer review journal articles. As Mr. Wilson may mention, the Center for Biologics Evaluation and Research does bench testing of the devices

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they regulate. These devices must meet certain laboratory criteria before and after licensure.

I thank you for your time.

I would like to introduce Mr. Len Wilson from the Center for Biologics Evaluation and Research who will conduct the next presentation.

**CBER Licensed Biological Medical Devices**

MR. WILSON: What I am going to attempt to do in the next 10 minutes is to give some historical perspective as well as accumulative logic behind where the Center for Biologics has been in regulating hepatitis test kits over the last 27 years.

[Slide.]

Hepatitis test kits B and C are regulated under the PHS Act and the FD & C Act. Now, I have put an asterisk on some of these slides. This was an afterthought in an effort to show some differences that exist based on the regulations, not necessarily on all policy, but based on the regulations, between what the PHS Act directs and the FD & C Act. With these test kits, they are licensed biologic medical devices, so they fall under both, but the PHS Act takes precedent.

The other thing to bear in mind is that these tests were originally licensed to detect hepatitis B, which

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had evolved from Australia antigen in 1972 to HBsAg, and it was targeted at protecting the blood supply when you had a 10 percent plus hepatitis B transmission rate in transfusions, this is the way the regulations were dealt with.

The FD & C Act, just as a point to consider, the amendments to the Medical License, Medical FD & C Act were not promulgated until 1976, so that you had a gap and the Public Health Service Act was used.

The tests are targeted at protecting the blood recipients from hepatitis B and C, and the objective is to identify marker-positive donations.

Now, the tests are largely weighted towards targeting silent infections. Most people are hopefully healthy blood donors and they come in fully expecting to be able to donate altruistically. The number of donations per year in the United States for transfusable products is approximately 12 to 14 million, it's a very large number.

The second point to bear in mind is that the intended use statements which are on most of these hepatitis test kits typically state for the detection of the marker, and this has been historically applied since the hepatitis B surface antigen test, which was the first one licensed in 1972, that was applied as the intended use statement, is

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largely carried through.

So, while the emphasis is on hepatitis B and hepatitis C screening of donors, these test kits were clearly used for the last 27 years in the diagnosis and monitoring of hepatitis B and C.

Anti-hepatitis B surface antigen was licensed in 1975. The weight of that licensure of that test kit was based on the standardization of hepatitis B immune globulin. It was not directly related to the determination of immunity relative to vaccination or other such clinical trials. It has been used for that, but that was not the original intent.

Antibody to hepatitis C was licensed in 1990, and anti-core, hepatitis B core tests were licensed in 1991 based on a recommendation by the Blood Products Advisory Committee in 1989 to increase the overall sensitivity for screening for hepatitis B.

[Slide.]

Of those four tests, two of them have second more specific tests. The hepatitis B surface antigen test has a confirmatory neutralization associated with it, there is none for the hepatitis B antibody test.

There is an immunoblot for the HCV antibody test, and there is none for the anti-core. Both of these types of

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tests are used relative to blood donations. When an individual test is repeatedly reactive on a screening test, then, they are tested with these two second more specific tests.

If they are negative, then, the donor is still deferred because the donor may be infected, but the gold standard in this case is time, time in terms of hepatitis B, wait eight weeks, and test for anti-core, as well as hepatitis B surface antigen again if the answers are negative, then, the donor is reentered, with HCV it is a six-month waiting period. If the individual then is negative after six months, then, is eligible to reentry as a donor.

[Slide.]

For the remainder of the presentation, what I am going to do is go through some of the technical aspects of the product approval process. Because these are licensed biologics, an IND must be filed by the test kit manufacturer, and they meet with us typically to discuss product design, clinical trial design, which typically includes comparator licensed test kits when they are available.

The first hepatitis C test, there was no comparator test, so we had to go deeper and deeper into the

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fundamentals of clinical trial design to ensure the safety and effectiveness of the test.

When the manufacturer develops the test plan, then, they file an IND which allows them to test the kit in blood establishments and they basically conduct a trial, and at the end of the process, they gather that data and they prepare a license application, product license application and an establishment license application.

The product license application has enough information in it, so that a person who is familiar with these manufacturing processes has enough information to be able to manufacture the entire test kit to specifications which the manufacturer has set, batch records for the clinical trial lots, clinical trial data, et cetera.

We are going to be moving in the future--well, let me talk about ELAs. ELAs are an establishment license. This is a separate license and it is essentially a paper review with an inspection, followed by an inspection of the manufacturing facilities.

All the manufacturing processes are basically locked in. Any changes that need to be made are made on a supplement basis, preapproval by FDA.

We are going to be moving to the NDA model of regulating these products and we are going to be calling the

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application a combined biologic license application in the future, so you will see that name every now and then come up.

[Slide.]

Product design considerations. Given the fact that we were dealing with not only blood screening, but also clinical sensitivity and specificity, these elements were traditionally part of the review of the product. In addition, analytical sensitivity and specificity was also heavily evaluated by our laboratory tests, as well as independent standards that may be available in the industry.

We also look at reproducibility. I have the two asterisks on equipment requirements and operator considerations because these certainly would be expected to be looked at to some degree in CDRH, in other words, can this test be run, you know, some of the basics, but the concern here is that we take an emphasis on these types of areas because, for example, platelets have a shelf life of five days. If the instruments or the operators can't run the tests, people are going to be seriously injured or die, so that there is an overriding consideration of the capability of being able to run this test. So, that is why we look at these areas also.

[Slide.]

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So, in sensitivity, what we essentially look at are disease populations, typically acute and chronic for hepatitis, and we are looking at generally several hundred. Typically, these are from repositories - high-risk groups, i.v. drug abusers, individuals with clotting disorders, dialysis patients. Typically, we look at approximately 50. Again, these would be compared typically to an already licensed test in most instances.

We also look at normal populations. Random blood donors are our basis target area, and depending on the marker, what we know about it, more about hepatitis B and less about hepatitis C, the number of donors which are tested can range from 10,000 to 30,000 depending on the circumstances of the test.

I would like to add also that one might look at that and say, okay, if you are checking a large population, why, it seems like more of a specificity study than a sensitivity study. Well, there are some crossovers because what we are trying to do is determine the sensitivity in the blood donor population. We know that the frequency of these markers and these diseases is extremely low, so it puts us at a handicap, so that is why we look at disease populations, acute and chronic, et cetera.

We also have a requirement basically that if a

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manufacturer is going to be conducting studies with an investigational test as compared to an already licensed test, and there is a discordancy, what we have asked is that the donor be parked for a while because we are not sure if that donor is really infected or not, this new test might be better, and what we ask the manufacturers to do is to conduct what we call discordant resolution, essentially to try to establish the true status of this individual, so that we can get a better link and stack the deck towards preventing transmission of these viruses in the blood supply.

In these cases, one would require linked studies. The followup is the best answer to determine if the person seroconverts. We also tell the manufacturer to throw everything they can at it, PCR, and the like, and validate those tests because we need to look at not only a PCR test, we need to know that the PCR test actually works and then we will take it into consideration in terms of trying to determine the true status.

All of this should be evaluated upfront. We tell the manufacturers, look, if you are going to be conducting these studies and you elect to link them, you need to tell us how you are going to resolve discordance because you are going to get discordance, you have to factor that into the

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equation.

If they don't elect to conduct the studies linked, i.e., being able to follow up with the donors, the result is the burden is on the manufacturer to bear the brunt of having a discordant potentially scored against them.

[Slide.]

We also look at analytical sensitivity, we look at comparative endpoint dilutions with already licensed tests, quantitative standards if they are available, hepatitis B surface antigen, there are some standards, there is PCR standards that are now emerging.

We look at seroconverting panels or the manufacturers do. These are commercially available seroconverting panels. These seroconverting panels are typically--and there is not a lot of them around--but they are typically developed based on inadvertent plasma donor draws.

In the plasma donation arena, a donor will come in and get bled for up to twice a week serially for an extended period of time. All the controls are in place to ensure the health of the donor, but the testing is ganged, so that at a certain point you go back and do all the testing rather than doing it every day. As a result, what you find is a series of positives, a series where a negative goes to a positive,

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so it is a clean seroconversion, and these panels are now commercially available, some for hepatitis B and some for hepatitis C.

These are used in the HIV arena. I have put it under the analytical sensitivity column, not so much because it isn't really clinical sensitivity, too, but it is to emphasize that we do a lot of statistical evaluation in an effort to use this in determining whether or not you have got a test that is a little more sensitive than another one, you know, statistically speaking.

Lastly, we have an asterisk. We have a CBER lot release panel. This is a reference panel, and all the hepatitis test markers have these panels released by CBER to the manufacturers, and they constitute approximately 10 specimens. There are a couple of negatives. There are selected diluted positives down to the lower limit of detection, which we feel is the appropriate level all things considered, and the manufacturers are required to pass this panel.

They are also required to test each lot against it. They are also required to take each kit lot that they are about to release, send it to CBER's laboratories. We test the same panel, look at their results, look at our results, and if everything matches, then, they get an okay

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from our quality control department that they may release that lot for shipment.

[Slide.]

Specificity. IVDs need to be evaluated for specificity, and clearly in the case of donor situations, false positives can cause a terribly, terribly difficult set of circumstances. Most people who are donors are altruistic and the last thing they want to do is get a letter from a blood establishment saying we think you may be infected with something, please go to your doctor.

This has very, very negative ramifications on the altruism of blood donors, so we need to make sure that the manufacturers of the test kits understand this, and essentially emphasize that the specificity of these test kits must be maximized, so we are looking at making sure that the specificity and the sensitivity of these test kits are absolutely maximized.

Again, the studies which we were talking about before, the 10- to 30,000 specificity evaluations, of course, are also integrated into those.

Related diseases are also evaluated. Hepatitis, for example, in the case of evaluating hepatitis B surface antigen, we would look at hepatitis A and hepatitis C specimens. These are typically repository, typically on the

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order of 10 to 25.

Unrelated diseases, infectious and non-infectious, EBV, CMV, as well as things like non-infectious liver diseases, biliary cirrhosis, et cetera, and typically, these are on the order of 10 to 20 samples.

What we are looking for is catastrophic, which we call catastrophic interference. If we were to ask the manufacturers to conduct studies to examine all of these things, nothing would ever get approved by FDA again, so we pick what we feel are the most appropriate related areas and emphasize those.

Analytical sensitivity. We look at subtype reactivity. In the case of hepatitis B, you are looking at ADNAY. In the case of hepatitis C, you are looking at core, NS3 and the like, interference studies, lipids, bilirubin, et cetera, and, of course, again the CBER panel.

[Slide.]

These are the areas of reproducibility, which are evaluated during the clinical trials. Typically, there is three sites, and the typical types of variance elements are evaluated. Each state is presented in a PI, package insert.

[Slide.]

The last two slides describe the review process, and here are just a couple of points. A committee is

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developed in CBER. The manufacturing process and the facility is evaluated, and the asterisk is over the facility because we have a separate license for the facility.

Typically, correspondence is exchanged.

CBER tests lots of reagents in the course of the product evaluation. There is a prelicense inspection which is conducted by CBER inspectors. These are the reviewers that actually review the product. The product is licensed, and there is a lot-by-lot release.

[Slide.]

Post-approval controls in place are lot-by-lot release, as I said earlier. There is a surveillance option which manufacturers can apply for, which allows them to periodically send in lots, however, they must still test every lot against the lot CBER panel and must pass that. As I said earlier, the inspections are conducted by CBER inspectors.

We have a unique situation where the blood banks are regulated by CBER, so we can generally pick up when there are problems in sensitivity and specificity right away, because of the need to get blood through the blood banks and out into distribution, and when there are problems, blood establishments pick up the phone and call us to report problems.

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Under the PHS Act, we have the authority to suspend or revoke a license immediately. I am not sure about recent changes to the medical device regulations for PMAs, but we have that authority. We also have the authority not to let release, so that is a control that we have on the manufacturers.

Thank you.

DR. THRUPP: Next, we have Dr. John Ticehurst.

### **General Concerns and Questions**

DR. TICEHURST: Good morning, everybody. Almost everything I have to present today is on slides, however, there are a couple of things I forgot to do.

[Slide.]

At yesterday's meeting that I realize all of you weren't part of, people introduced themselves, so I thought I had better make an overhead to introduce myself. I am a medical officer in the Microbiology Branch of the division that Dr. Gutman runs, and also a part-time assistant professor in Medical Microbiology at Johns Hopkins. That serves to just let you know that I do get an opportunity to try to keep up to date and participate in some laboratory practice and also that, indeed, Dr. Charache and I have met.

In addition, you will notice that long string of titles I have there. This is a reflection of my English

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heritage. I have this genetic need for titles. The F.M., the one after M.D., is I was elected as of February 1st as a Fellow of the FDA Academy of former interim Microbiology Branch chiefs.

[Slide.]

The material I am going to go over in the slides today are essentially what the panel members received last week with a few corrections and some condensations.

To reiterate what Dr. Gutman mentioned a few minutes ago, the first point is that we are seeking the panel's advice with regard to appropriate, least burdensome --and "least burdensome" is wording that comes right out of the FDA Modernization Act of 1997 that Dr. Gutman was referring to a few minutes ago--types of clinical data and information that should be submitted for establishing assay performance.

Because the number of indications and analytes is large and the panel received several tables we put together that sort of give a take on all the different permutations of indications and analytes for these three viruses, and we have one day for discussion, we have selected several examples that represent our key concerns and questions about these assays, and we think, as Dr. Gutman mentioned, this can be a starting point we can hopefully extrapolate from

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some of your advice and eventually it won't surprise us if we see assays for HDV, HEV, maybe HGV, and so forth. We can extrapolate there, as well, and we will get you all back together.

These general questions that I am going to go over in the next few minutes are going to be presented now, but we are going to discuss them at the end of the day. They are being presented now sort of to seed you. I think given the hour, I am also going to test your short-term memory.

We won't really discuss them now, but there will be context after which we will have sessions on HCV, HBV, and HAV, and the reason they are being done in that order is that I feel that HCV is probably the scientifically most difficult one, and want to get you with that one when everybody is freshest in the day, and HAV presents the fewest scientific questions.

In addition, I wanted to bring up that we asked Mr. Simms and Mr. Wilson to give their presentations to give some background. We are not being asked to provide regulatory advice, but you are being asked to provide scientific advice.

We want to give you an idea of the regulatory constraints that we are under in the Center, the kind of approaches that we have used for Class III devices

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traditionally that are actually required by policy, regulation, and law, and the kinds of things that we don't have that the Center for Biologics does have in terms of having control over devices that they license.

[Slide.]

I am going to see how fast I can read through these and, please, if I am reading too fast, let's stop, but we want to get on to the public discussion.

[Slide.]

What types of studies are adequate, first, for assays that are well understood, for primary indications that are well established, or for secondary indications? An example of a primary indication like this would be HBsAg testing during pregnancy. The purpose of it is to identify neonates at risk. My colleagues from CDC tell me that all neonates are essentially vaccinated in the delivery room and the question is what more is going by giving them hepatitis B immune globulin right after birth.

An example of a secondary indication would be total antibody to hepatitis B core as a secondary marker for acute or chronic hepatitis B infection.

When testing can be repeated on a subsequently collected specimen, in an effort to confirm specificity of a positive result or to overcome recognized deficiency in

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sensitivity.

The first point refers to the concept that most patients can be seen more than once. Most blood donors, you have to make a decision on them at one point.

The second point would refer, for example, to the total antibody to hepatitis C virus. Biologically, people don't develop antibody until some point, and as each generation of assay has been developed, the antibody can be detected earlier and earlier in the course of infection.

When results from two or more assays should be combined for one indication, thus lessening the concern about the sensitivity and specificity of each.

I am sure there are complicated statistical approaches to these, but just when you think about it, there are six or seven markers for hepatitis B virus that could be applied in any given point in time, particularly in an acute and chronic infection, and can be used essentially cross checks on each other.

[Slide.]

What types of studies are adequate for characterizing performance in certain special populations, such as coinfecting patients? It has been recognized for years, for example, that patients who are chronically or acutely infected with hepatitis B virus, when they are

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coinfected with hepatitis D virus, it changes the pattern of markers.

What about people with altered immunologic responsiveness, leading to atypical assay results which is biologically atypical, not a problem with the assay itself, and potential for misdiagnosis?

An example of that would be the changes in markers of particularly for hepatitis B and patients with AIDS.

For assays that were recently developed, so that safety and effectiveness have not been determined but for which potential indications could have significant public health benefits?

For example, this would be assays for quantifying HCV RNA.

[Slide.]

What about FDA approaches to understanding safety and effectiveness? As Mr. Wilson indicated, FDA has a long and successful history of evaluating assays for blood product safety.

The approach to establishing performance for detecting HBsAg, total anti-HBc, and anti-HCV has emphasized, as he pointed out, very high analytical and clinical sensitivity, and comparison between new and previously licensed assays by testing many thousands of

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specimens.

He also indicated--which I didn't put on here--they have a lot of different controls that have nothing to do with the paper evaluation of the assay that we don't have at this Center.

[Slide.]

For which assays and which diagnostic and monitoring indications in this approach of emphasizing sensitivity and testing lots of specimens, when is it appropriate, and when can it be used with less burden, that is, less data? When is it not appropriate, and what then should be emphasized in that case, for example, specificity or clinical endpoints?

[Slide.]

Serially collected versus single specimens. Performance characteristics and accurate interpretation of results are affected by the ability of different qualitative assays--for the same analyte--to detect temporal patterns of waxing and waning that may occur either during or after the course of infection or in response to immunization.

We believe that this consideration could apply to any of the markers that we are talking about today with the exception of total anti-HAV, but it pertains particularly to IgM anti-HAV, IgM anti-HBc, HBsAg, and anti-HCV, and

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particularly when they are indicated for virus-specific diagnosis of acute hepatitis.

[Slide.]

Along the same thought line, serially-collected specimens, one form of which Mr. Wilson referred to as seroconversion panels, are essential for determining the activity with reference to these temporal patterns, but often it is very difficult to obtain such specimens either from archives, as Mr. Wilson mentioned from commercial sources or a company's own sources or university sources or from new studies. A lot of times it is very difficult to recruit patients for a new study.

[Slide.]

On the other hand, performance can be estimated by testing a collection of single specimens with new and older assays and then comparing the results. This is what Mr. Simms referred to as device-device comparison.

The accuracy of such estimates is high when a new assay is compared with a reference assay, but we are not aware of any appropriate reference assays in this field.

Accuracy is likely to be high when the new assay is compared with results from indicated assays for two or more analytes, and that opportunity is available, for example, for hepatitis B when coupled with pertinent

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clinical information.

A way of looking at this would be by taking the results that are right at hand and can be pulled out of laboratory and patient charts retrospectively rather than having to plan on collecting these things in a prospective manner.

[Slide.]

When are serially-collected specimens necessary? On the other hand, when is it sufficient to compare results from a new assay either with those from one currently marketed assay for the same analyte, device-device comparison, or an approximation of diagnostic truth that is based on all lab data generated from that specimen according to the physician's orders who is taking care of the patient and also readily available clinical information?

[Slide.]

Types of specimen collections. We feel that specimens collected in new, well-controlled studies are likely to be subject to less bias than specimens in archived collections. This pertains to a lot of the discussion that went on yesterday.

However--this is one thing that wasn't brought up yesterday--such studies are expensive and they may take years to perform, and it may be difficult to recruit

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patients who meet appropriate inclusion criteria. The question then is for which analytes and which indications are new studies essential.

[Slide.]

Going back to one of Dr. Gutman's points, if new studies are essential, when should they be done, which should be performed before an assay is considered for approval, what we refer to as "premarket," and which could be performed following conditional approval as a condition for full approval, "postmarket" studies.

[Slide.]

Before too much time in the day passes, I want to say thank you and also apologize. I want to thank the panel for coming and wrestling with all these thoughts today and particularly for Drs. Hoofnagle and Hollinger joining the group, and I want to apologize to you personally for the delay. We sent materials to you very late last week. Some of that is my fault, and I am sorry for that.

There are a number of colleagues in the branch who have been of enormous help to me in getting these materials ready, as well as some folks elsewhere in FDA, and thank all of you for participating. I am sure we will get some good comments from all of you. I think at least my family needs an apology and a debt of thanks for the time I have been

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serving the public over the past few weeks.

Thank you very much.

DR. THRUPP: Thank you, Dr. Ticehurst.

### **Open Public Hearing**

DR. THRUPP: At this time we would like to call for the open public hearing. We first would like to hear from those who have communicated with the FDA that they have comments to make.

We have one that is on the agenda and another one that didn't get into the agenda. The first is Carolyn Jones from HIMA, and secondly, Matt Klamrzynski from Abbott. After their presentations, we can call for comments from any other members of the public that are here today. First, Carolyn.

MS. JONES: Good morning. I am Carolyn Jones. I am Director of Technology and Regulation with the Health Industry Manufacturers Association.

HIMA is a Washington, D.C.-based trade association that represents over 800 manufacturers of medical devices, diagnostic products, and medical information systems. Our members manufacture nearly 90 percent of health care technology products purchased annually in the United States and more than 50 percent of those purchased annually around the world. For many of our members that manufacture

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hepatitis assays, this panel meeting raises important issues.

Due to the limited time we have had to prepare for this meeting, the primary focus of my comments will be the evaluation methods for the established HAV and HBV antibody tests. Issues related to antigen or nucleic acid tests for HBV or HCV will be addressed more fully after industry has had the opportunity to digest the information from this meeting and gain a better understanding of the agency's focus and direction in relation to these technologies.

We really do support the development of new guidance documents and/or review criteria for hepatitis tests. HIMA would like to commend CDRH and particularly the Microbiology Branch for scheduling this open public panel meeting to gather additional scientific advice and recommendations from the panel on appropriate evaluation strategies to demonstrate the effectiveness of both novel technology and established hepatitis diagnostic products.

We also appreciate this opportunity to present industry comments. Technology is changing and it is appropriate for FDA to recognize the need to develop guidances that explore new ways to help manufacturers demonstrate the effectiveness of new and established technologies.

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We think it is important that FDA and industry work together to develop clear review guidance for hepatitis assays intended for diagnostic use.

We hope that following this panel meeting there will be an opportunity for additional meetings with industry and other experts to expedite FDA's development of new guidance documents and/or criteria for review of hepatitis assays intended for diagnostic use. Industry needs uniform guidance and advice on FDA's current requirements.

The rapid development of such guidances for FDA reviewers and manufacturers will assist all parties in meeting our respective goals: for FDA, the goal of timely premarket reviews mandated by the FDA Modernization Act of 1997, and for manufacturers, the goal of timely introduction of safe and effective new products. We believe that these goals can most effectively be achieved by a collaborative effort between FDA and industry.

Once new guidance documents are available to industry for the various hepatitis markers, including clear advice on sample size requirements and methods of discrepancy resolution, there should be little need for costly advisory panel meetings to review standard applications for HAV, HBV, or HCV tests.

These will be evaluated according to uniform

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evaluation and review guidance jointly developed and agreed upon by FDA and industry. This will allow all parties, FDA's Microbiology Branch, its advisory panel, and industry more time to focus on the evaluation of new technologies or novel diagnostic markers. This is consistent with the goals of the FDA Modernization Act.

Just a little perspective on FDA's review of hepatitis. Len did an overview of CBER's handling of these products.

Until very recently, new HBV antibody test premarket applications for both blood screening and diagnostic products were reviewed by CBER with a few exceptions. The first of the hepatitis screening and diagnostic tests was licensed in 1971 for the detection of hepatitis B surface antigen in serum or plasma.

Both CBER and CDRH hepatitis premarket clinical test requirements have traditionally focused on analytical comparisons to currently licensed or approved tests in random blood donors and in well-characterized patient populations with both acute and chronic HBV infections, as well as in those with other viral infections.

Discrepancy testing has been allowed for new evaluations by both Centers, along with recomputations of sensitivity and specificity after discrepancy testing with

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additional and sometimes more sensitive methods and/or after additional clinical parameters are discerned.

Test performance results after discrepancy testing have traditionally been allowed in the final labeling claims for new diagnostic tests. Considering yesterday's panel discussions, we believe this issue should be discussed further before FDA develops guidance that addresses resolution of discrepant test results.

For HAV tests, these tests have been similarly evaluated and approved by CDRH, with reliance on analytical performance and comparisons to approved commercial tests, along with allowances for discrepancy testing.

For antigen or nucleic acid test evaluation, in principle, these tests can and will be used for similar purposes and in the same manner as HAV, HBV, and HCV antibody tests. Although these tests directly detect the presence of nucleic acid sequences from the virus, if they are used as an aid in the diagnosis of infection with the respective organism, they are similar in purpose to the antibody tests and can and should fall under the same clinical study requirements as the antibody tests.

Only when these tests are used for non-diagnostic purposes, that is, monitoring the anti-viral effects of drug therapy for identification of known drug resistant strains

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or for genotyping, should clinical study requirements differ from those applied to the antibody tests be considered.

Discrepancy resolution schemes for these tests should be carefully worked out in advance by industry and the agency. In particular, for amplified nucleic acid tests, reliance upon unapproved but well documented discrepant test methods, such as alternate nucleic acid testing, will be essential in the evaluation of the clinical performance of these products.

In summary, we believe the historical philosophy of both CBER and CDRH in clinical evaluation requirements for hepatitis diagnostic tests has been based on the fact that the hepatitis markers and seroconversion patterns, at least for HAV, HBV, and to a lesser extent HCV markers, are well understood in the medical community.

Indeed, this is clearly referenced in the 1991 CDRH draft review criteria documents for both HAV antibody tests and for HBe antigen and antibody tests. Thus, somewhat more limited clinical testing for diagnostic indications, which focuses on the analytical comparisons of characterized patient samples showing substantial equivalence in results, has been historically considered sufficient for approval or clearance of these tests.

We note that only a limited analysis of

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longitudinal seroconversion sample panels have been historically required by either CBER or CDRH to verify, not to validate statistically, the new test's ability to assess marker progression throughout the course of disease. CBER and CDRH have normally requested 5 to 10 seroconversion panels to be tested and both Centers have been sensitive to the difficulties of obtaining such seroconversion panels.

Almost all currently approved and licensed diagnostic tests for the detection of antibodies to HAV and HBV have been evaluated in the above way. We are unaware that this has led to public health concerns on the utility of the current commercial hepatitis diagnostic tests.

As such, HIMA members concur with the above equivalence or analytical comparison approach to the clinical evaluation of new hepatitis antibody tests, and believe it is supported by information in both the medical and scientific literature, and meets current regulatory requirements to find the least burdensome method to assess the effectiveness of new devices, as mandated by the FDA Modernization Act.

We do not believe it is appropriate to request that each manufacturer demonstrate the clinical utility of well-known hepatitis markers. The benefit to the public health would be minimal, and the cost to industry

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significant.

We do have a few recommendations. On behalf of the members that manufacture hepatitis products, we ask the panel to recommend that FDA work closely with industry, clinicians, and the laboratory community before it requires changes in the clinical evaluations for demonstrating the safety and effectiveness of hepatitis assays.

Additionally, we recommend that FDA not dictate which markers must be used together to determine a clinical diagnosis. That should remain in the realm of practice of medicine, specific to a physician order or laboratory policy.

To assist in the development of new and revised guidance documents, we recommend that FDA consider the following standards of practice in the evaluation of new hepatitis diagnostic tests:

FDA should continue to allow hepatitis marker evaluations for diagnostic indications to focus on new device or approved or licensed device comparisons using patient samples supplemented with other relevant analytical test results.

FDA should continue to allow discrepancy resolution as discussed in the CDRH 1991 HAV and HBV draft review criteria documents. The agency should allow

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computations of sensitivity and specificity in final labeling claims to reflect resolution of discrepant with a third resolution test method or additional clinical information, including other hepatitis markers and other clinical information.

FDA should allow the use of single timepoint or serially collected patient samples to come from archived sample collections, as has been historically allowed in IVD evaluations. FDA requests for evaluation of seroconversion panels should be minimal and only used for verification of marker pattern test results in comparison to an approved test, not full validation.

The FDA should also continue to accept the use of both U.S. clinical data and data developed in foreign clinical trials as discussed in the above mentioned 1991 draft. The foreign studies should be well-controlled and conducted per U.S. requirements using product of finished manufacture quality.

FDA should also allow diagnostic indication statements for hepatitis markers to remain more generalized, as has historically been the case. Using a licensed HBsAg indication statement as an example, the indication statement would indicate that the tests can be used also as an aid in the diagnosis and management of patients infected with

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hepatitis B virus infection.

Any new or revised hepatitis guidance documents should state clearly the minimum number of known positive and known negative patient samples which must be tested by both the new and approved comparative tests.

FDA should look to national and international standards and/or performance panels for new hepatitis tests to minimize the clinical evaluation study requirements.

We in industry are ready and willing to work with FDA and this panel in developing appropriate regulatory strategies for the regulation of hepatitis diagnostic products. We know that these issues will not be resolved today, but look forward to a cooperative effort to bring resolution to these important issues in the near future.

Thank you.

DR. THRUPP: Thank you, Carolyn.

The next speaker is Matt Klamrzynski from Abbott Laboratories.

MR. KLAMRZYNSKI: Good morning. Abbott Laboratories thanks FDA for the opportunity to address the panel. We support the HIMA comments that you have just heard and very well articulated by Carolyn Jones and really have nothing to add.

We felt it would be beneficial for the panel,

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though, to hear more regarding the practical aspects of test evaluations in keeping with the spirit that we have heard here of less burdensome methods that FDA had codified in the recent Modernization Act.

We have asked that a hepatologist, so that you can get a medical perspective, scientific, you have heard industry, you have heard FDA, address the panel during the time allotted for our five minutes and to provide more insights on evaluation issues.

I would like to introduce Dr. Dwain Thiele, Professor of Internal Medicine, from the University of Texas, Southwestern Medical Center. Dr. Thiele has provided Abbott with well-characterized pedigree specimens for evaluation of our tests and continues to do so.

Dr. Thiele.

DR. THIELE: As you have been told, my current position is as a faculty member at the University of Texas, Southwestern Medical School, in Dallas.

Over the past 18 years I have been at that institution. My primary clinical responsibilities have been to serve as a physician in an outpatient liver diseases clinic and as an attending and consulting staff physician in inpatient services at Parkland Memorial Hospital, which is a major teaching hospital and is the only county and public

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hospital in Dallas County, Texas.

Throughout that time interval, we have, and continue to care for, a fairly large number of patients with all types of chronic and acute viral hepatitis.

Just to clarify my relationships with Abbott Laboratories, during the past at least seven years I have, both as a scientific collaborator and as a paid contractor, obtained various clinical specimens from these patients that have been used both in research studies and to validate new serodiagnostic assays.

During the past several months and increasing the last several weeks, I have been asked repeatedly for advice regarding the practicality, feasibility, and importance of obtaining certain samples and clinical data in a prospective fashion to better validate these sorts of tests.

I think there are certain aspects of the way we deal with these patients in 1998 that are pertinent to this issue. With respect to chronic hepatitis B and chronic hepatitis C in particular in patients who are biochemically and histologically active disease, because we currently have treatments available and because there are major implications to the patients' well-being, these patients are seen frequently by physicians. They are usually very interested in participating in investigative research

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studies, and I think these sorts of patients more so than ever are probably available for obtaining serial specimens and well-characterized specimens for these sorts of studies.

In contrast, the way in which we manage patients with acute viral hepatitis has changed over the years. When I began my training now some 20-odd years ago, the only serodiagnostic test available was a test for B surface antigen, so in most patients with acute viral hepatitis, or with many patients at least, the diagnosis was ambiguous, and the center of practice for those patients was to often hospitalize them acutely during their illness and to see them frequently in followup until their illness resolved, determined whether or not they are going on to chronic infection.

In 1998, because of better serodiagnostic and better understanding of the disease, for at least those patients with acute A or acute symptomatic B, the number of visits and the degree of followup has changed considerably.

Hepatitis A is an infection that does not cause chronic liver disease. Most of the patients that I see with acute hepatitis A, by the second or at most the third visit are already clearly improving, and at that point we do not schedule additional followup visits for medical indications.

If there were a perceived need, I am not quite

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sure what that need might be to get multiple serial bleeds in those sorts of patients, we would be asking patients to make special visits for the purpose of studies only, and this for many of our patients would involve loss of work time, and so forth, so it would be a major practical issue.

With respect to acute hepatitis C, again, the clinical setting is quite different. This is an infection that very commonly progresses to chronic liver disease. Again, we have therapies available, and also because of some problems with sensitivity of the assays and some difficulty in distinguishing acute and chronic infection, serial followup is both medically indicated as part of our standard practice and I think should clearly be part of any evaluation of new tests.

But I think the major issues in assessing utility of diagnostic assays in evaluating patients with acute viral hepatitis has to do with how sensitive they are very early in infection. This has been pointed out repeatedly with acute hepatitis C in which the initially available reagents were often negative at the earliest timepoints in disease, only later became positive, but those types of patients largely came from a different era, an era in which many patients developed disease as a result of transfusions in which either in routine clinical practice or as part of

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prospective studies, one could prospectively accumulate samples that would reasonably include some patients who were seroconverting.

At present, because of advances in our testing and blood banking practices, we just don't see those patients. Most patients are either sporadic cases or more commonly from injection drug users who only come to medical attention after they develop symptoms.

There may be ways to prospectively evaluate those patients, but would involve major efforts to do prospective epidemiologic studies in those communities.

With respect to A and B, I don't know of any way that one could really ethically accumulate new large seroconversion panels because we have good vaccines. We have excellent vaccines for both A and B, and so if you have identified a patient as being at high risk for developing those diseases, the appropriate medical practice would be to vaccinate them, and they would then not be available for following prospectively, develop new seroconversion panels.

So, I think in deciding what sorts of things are practical or feasible, as far as validating tests and with respect to their utility in acute viral hepatitis, these sort of issues need to be taken into consideration.

Thank you.

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DR. THRUPP: Thank you.

Do we have other participants in the audience that would care to add any comments at this point? I don't see any hands and I don't see anybody jumping to their feet.

I think that we can take a five-minute break and then reconvene for Dr. Ticehurst's presentation on hepatitis C.

[Recess.]

DR. THRUPP: As part of the open public hearing session, we like to provide the opportunity for panel members to ask the previous presenters if there is any questions or additional comments, so we would ask that the panel members consider any other thoughts they might have that either Carolyn Jones or Matt Klamrzynski could respond to.

Dr. Charache.

DR. CHARACHE: I do have a request for clarification from Carolyn Jones, if she is here.

I think Carolyn already knows this, but I will give you my bias. I do not like regulations. I believe in regulatory lite, spelled l-i-t-e. But the brew has to still taste good.

I had two questions for clarification. You made the point that HIMA would come back with recommendations and

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advice pertaining to newer technologies, such as the molecular technologies, hepatitis C virus, and other viruses which are more advanced.

I am assuming that the same reservations about future advice would pertain to the advice from the Microbiology Panel, as well.

MS. JONES: Yes.

DR. CHARACHE: I am thinking, for example, for the statement at page 6, "Any new or revised hepatitis guidance documents should state clearly the minimum number of known positive and known negative patient samples which must be tested"--just as an example. Clearly, that will be a function of the nature of the test, the technology used, and what the concordance is as you develop the test.

So, I am presuming you wouldn't require that in the initial guidance.

MS. JONES: No. I think the point that the manufacturers would like to stress is that we do think this should be a collaborative effort and we don't think that all of these issues can be resolved today, and we just want to put it on the record that we think this should be an ongoing collaboration between this panel, the FDA, and industry to get these issues resolved. I don't think they are unresolvable, but--

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DR. CHARACHE: The other clarification pertains to the statement that once there are guidance documents developed by industry and the FDA, there would be little need for the advisory panel to review applications and standards.

MS. JONES: We are talking about the standard applications. We think that your time and FDA's time, as well as industry's time, should be focused on the new and novel technologies, the new things that are coming on the block, that once we resolve these issues, those types of products won't have to come to the panel anymore, FDA will have had the experience, industry will have had the experience, and we would have all had your input.

DR. CHARACHE: But my concern and the reason I am asking for clarification is that the definition of the word "standard" is sometimes in the eye of the beholder, and in addition, the use of the product and the information provided to the clinician and the laboratorian who has to use it is an important component in terms of what kinds of groups of patients or technologies for assessment you may want to apply, so I am hoping that HIMA is not suggesting that if industry and/or the FDA would like advice from an objective outside panel, that HIMA would not be opposed to that.

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MS. JONES: Oh, we would not, and we understand, when we speak of the standard technologies, we are talking about things that we have a known intended use, known indications for use. When those things change, the playing field sort of changes, and we would expect for FDA to come back to the panel or come back to industry and have additional questions.

DR. CHARACHE: So, you would leave the decision on how to use the panel up to the FDA?

MS. JONES: Yes.

DR. CHARACHE: Thank you.

DR. THRUPP: Dr. Zabransky.

DR. ZABRANSKY: Carolyn, I would like you to perhaps either clarify or to indicate your distinction on page 6, you mentioned in paragraph c, you indicate or differentiate between verification and validation.

Are you using the same terminology here as is promulgated by HCFA, that is, verification is, as you say here, comparison between the approved test and perhaps a clinical condition, but validation is only the continued certification that the test is performing as originally established, or are you using some other definitions?

Some people use these terms interchangeably, and they should not be. That is the point.

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MS. JONES: I have to admit that that is not my language there, and I am not really clear on the distinction, but if I look at it from an industry perspective, broadly, we would be looking at it from a CLIA definition.

DR. THRUPP: Are there any other questions from the panel for the previous presenters? Dr. Hollinger.

DR. HOLLINGER: Also, on page 5, at the beginning of the recommendations, you say something to the effect that, "We recommend FDA not dictate which markers must be used together to determine a clinical diagnosis."

Could you amplify on that a little bit, what you mean by that?

MS. JONES: Well, that observation came from some questions that was on the Internet before this meeting, and there was some indication in one of the questions that FDA would be asking this panel to suggest that certain products would be used in combination to make the clinical diagnosis.

We think that while that may be an interesting discussion, we think that that pulls something away from the practice of medicine, from the physician's purview, and we think that should be outside of the determination of the requirements, submission requirements for these products.

DR. HOLLINGER: The other question is often

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physicians don't know why you would ask for some duplicate tests done for validation of a previous test, and I think it is something that probably should be discussed at the panel today.

DR. THRUPP: Dr. Hollinger, you would imply that the package insert at least, whatever may or may not be done with that, should likely include recommendations concerning which markers are most relevant?

DR. HOLLINGER: I think there are certain tests that could be done together that would be useful in diagnosis, yes, and I think that is a possibility and I think it should be discussed.

DR. THRUPP: I am not sure that the package insert in the practice of medicine would be construed to be dictation because as we all know, the package insert recommendations are often in the practical world not necessarily followed, but I am not sure that we would want to say that the FDA not include recommendations in the package insert. Whether you call those dictates might be semantics.

MS. JONES: It is not for lack of FDA and industry trying to get people to read those package inserts.

DR. CHARACHE: I would also support that very much because I think if the information is in the hands of the

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laboratorian who is using that test, they serve as a reservoir of information for the practitioner. There is no way that a practitioner can understand the purpose and the best use of every test that the FDA has approved.

MS. JONES: But I think in that section, I did indicate "and laboratory policy."

DR. THRUPP: Any other comments?

Let's call Dr. Ticehurst back to lead us into hepatitis C.

#### **FDA Presentation**

#### **Hepatitis C IVD**

DR. TICEHURST: Hello again. Before I talk about hepatitis C, I would like to make two announcements. One is that during the break, that table moved and there were some papers on it that were near and dear to me, and I would sure like to have them back. They have disappeared, and I would appreciate that.

The second is to correct the record. In Ms. Jones' presentation, she referred a number of times to draft guidance documents that had been prepared by this Center for assays for hepatitis A virus and for hepatitis B virus e-antigen and its corresponding antibody. Those documents have been outdated, they are no longer in distribution, so they are not considered to be relevant documents, and I

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would appreciate it if the panel would understand that.

[Slide.]

In the material that was sent to the panel, the first section for each virus was headed with general questions. In an effort to avoid more semantic confusion, I have retitled these as general issues, and there are a lot of questions that come up in these general issues. I would consider these queries that we have been considering as we have been wondering about how to approach the assays for these viruses.

The panel is welcome to address any of them that they would like to, but I think if we addressed each one of them specifically, we would have to be calling in for dinner for the next three weeks. So, we will have some much more general questions at the end of each section for the panel to consider. Again, we have picked specific examples that we think represent key points of concern for us.

First, this is under the category of testing algorithms for diagnosis of hepatitis C or HCV infection.

The traditional testing algorithm for anti-HCV--and Mr. Wilson referred to this--uses two steps. He didn't use quite this terminology.

The first step is usually an enzyme immunoassay, and that specimen is initially tested as a single specimen,

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if a negative result is obtained, the testing stops at that point. If it is positive, it is retested in duplicate, and if both duplicates yield negative results, the testing stops.

If, however, two out of three or three out of three are positive, it goes on to the second step, which is an immunoblot-like assay. When you think about this, really, the first step, any result that is over a certain analytical threshold or cutoff is considered to be an equivocal result.

The first question in regard to this: Is this algorithm necessary when an assay is indicated for diagnosis of acute or chronic hepatitis C?

[Slide.]

Here are some examples of alternatives to such testing. An assay for HCV RNA could be indicated as a first or second step assay for diagnosis. This is, in fact, what we use at Johns Hopkins as a second step assay for diagnosis. It's a home brew assay.

An enzyme immunoassay could have a more traditional equivocal zone that would achieve analytical sensitivity at least that of assays licensed for blood product safety, which would ensure retesting of all specimens that yielded equivocal results, and a cutoff or

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cutoffs that would yield clinically specific results according to risk, thus eliminating the need for retesting when positive predictive value is high.

There is two questions that come out of that, is why bother, why rock the boat? You know, the system has been set up for blood product safety and having different cutoffs and things could be very confusing.

Those of us that were at the NIH consensus conference on hepatitis C in March of '97 heard over and over about problems with assays for hepatitis C virus infections, one of which was problems with predicted values with the antibody assays, and this would be one way to address those. The types of claims that are made, of course, are up to the manufacturer.

[Slide.]

Perhaps a more difficult question would be what type of testing algorithm, if any, would be appropriate for a first-step assay for antibody to hepatitis C virus when it was intended for use in a low-complexity laboratory such as those in physicians' offices.

We have been getting inquiries about these types of assays, and consider how these might be used and whether we should be considering such claims.

[Slide.]

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The second general issue is establishing performance of assays for HCV RNA. There are at this time no approved or licensed assays for detecting or quantifying HCV RNA, and that applies for all the nucleic acids of the three viruses that we are discussing here today, so we will use HCV RNA, and we will talk a little bit about HBV DNA later.

However, I don't think it will come as a surprise to anybody in this room that detection, if not quantitation of HCV RNA is a standard or practice at this point. It is certainly the only practical analyte for direct evidence of HCV replication, and it is an important criterion for monitoring HCV infection whether or not the patient is being treated with antivirals.

[Slide.]

Before too long, I think we are going to be seeing some premarket approval applications for these types of assays, and there are a number of questions that we have been thinking about. This goes back to a point that was just discussed.

What types of standards, whether they are material or written--by that, material, I would mean perhaps a standard preparation of HCV RNA or cloned to HCV cDNA--that could be used as a standard for ensuring performance, or

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written, such as a written guideline, and I will remark that I don't think there are any appropriate material standards at this point.

There is a group in Europe that has been developing a standard of multiple HCV genotypes for plasma product safety. I don't think this is applicable to individual patient diagnosis. There are no written standards.

There is an NCCLS document for qualitative assays for detection of nucleic acid for infectious diseases. There is a subcommittee that is developing such a document for quantitative assays.

With regard to these types of standards, first, is there a criterion for analytical sensitivity that should be met? In other words, is there a clinically significant cutoff that all such assays should meet or should there be different cutoffs for different indications for use?

Anybody that has performed a PCR assay knows that it is particularly difficult to achieve precision or reproducibility with assays that are based on amplification of nucleic acid.

By saying "PCR," we know that those patents that are owned by Roche were referring to any of the various varieties of amplification.

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What approaches, such as proficiency criteria for the laboratories that are participating in the clinical studies that will be supporting an HCV RNA assay, should be used to minimize the effects of analytical variables in clinical performance?

For quantitative assays, is there a clinically significant range over which a criterion for precision should be met? I am not even going to ask what that level of precision should be. I think those of us that have seen data on a number of these quantitative assays knows that it is very hard for them to be precise.

[Slide.]

It goes without saying--well, we will say it--it is difficult to obtain or characterize large quantities of HCV RNA from virions. As many of you know, HCV RNA does not propagate in cell culture, at least not in any practical way. The only way to propagate it is to put it in a human or a non-human primate.

What are appropriate positive controls and calibrators for accurately detecting the wide range of genetic variation among different strains of HCV?

These are extra questions that were added to the material that was sent to the panel.

Second, what matrices should be considered, and

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these include serum, plasma, whole blood, white blood cells, or liver tissue, for example.

Lastly, what types of studies should be done, if any, for diagnosis and monitoring of HCV-infected infants? The antibody assays are useless in them.

[Slide.]

Another consideration. As I mentioned before, there are no approved assays for HCV RNA. Should unapproved assays be used as a criterion--not the only criterion--but a criterion in analytical or clinical studies for determining performance of HCV-specific assays?

If so, what performance characteristics should be established for such an unapproved assay?

This is a real chicken or egg problem. How do we figure out how well an HCV RNA assay is doing if we can't compare it to the only other analyte that we can follow, but if that assay isn't approved, how do we know it is good?

I don't think it is fair to ask a company to prove that the assay that they are using for comparison should be subject to the same criteria for approval as the one they are trying to sell.

[Slide.]

Moving to a different subject. Let me discuss a couple of indications for use here. Again, it is key

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examples.

The first would be diagnosis of chronic hepatitis C by detecting antibodies to HCV. These are some criteria that could be considered in studies for determining the performance of a new assay. I am wondering if these would be appropriate.

Again, this would pertain to specimens that are being tested with the new assay, that these data would be available for the patient from whom that specimen was collected. That patient would have had positive results from two serum specimens collected with an interval of at least six months from two-step testing with comparative assays for anti-HCV.

Signs or symptoms of hepatitis and biochemical evidence of hepatitis, if present, and for the time being it would be optional to have detection of HCV RNA at any time during the study. I would think that once we have approved HCV RNA assays, that this would be reasonable to consider as a criterion that the patient has hepatitis C.

Another optional criterion would be, if indicated, histopathologic changes in liver tissue collected at any time during the study, changes that would be consistent with chronic hepatitis C.

[Slide.]

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Now, how can we look at monitoring? Currently available tools include laboratory assays, both research, and clinically available, and then those would include assays for the number of different states of HCV RNA, either qualitative or quantitative testing, testing for HCV genotype of which there are also no approved or licensed assays, and what is now strictly a research arena, testing for the swarm of HCV types within a patient, referred to as quasispecies.

There are also non-approved assays that detect antibodies to amino acid sequences that are thought to be specific for certain genotypes of HCV. A number of research laboratories are detecting evidence of cellular immunologic responses to either the infection or associated liver disease.

[Slide.]

Other markers can include biochemical markers, such as ALT histopathologic assessment of liver tissue, assessment of the state of the virus in liver tissue, particularly as the disease gets late, various imaging techniques for the disease, and, of course, the traditional symptoms and signs of disease.

[Slide.]

When we get to the discussion, we request that the

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discussion be focused on the appropriate types of clinical studies for determining performance of assays for these different states of the HCV genome assays in either serum or plasma.

There are a number of different formats for these types of assays at this point. One is detection of HCV RNA qualitatively, another is quantitative detection of HCV RNA either by direct hybridization followed by amplification of the hybridization signal, by amplification of cDNA, which would be the method most used for qualitative detection, by detecting HCV genotype either by appropriate detection of nucleotide sequences whether by sequencing or by using hybridization probes to detect certain genotypes or by the antibodies I just referred to, and the other state that I also referred to a minute ago, the detection of quasi-species in patients at different stages of their infection.

[Slide.]

So, the question to consider then becomes: What are the monitoring indications for HCV-genome assays? There could be a number of such indications.

They could include the state and severity of virus-associated disease at the start of the monitoring period. They could include the prognosis for the patient

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without antiviral therapy including the likelihood of "recovery." I put "recovery" in quotes because I don't think anybody knows if there is a state of true recovery from HCV infection at this point.

It could include the prognosis for progression to chronic disease including the type of chronic disease and the rapidity of the progression.

[Slide.]

Other possible indications would include the patient's progress if antiviral therapy were started, again, the likelihood of response to therapy. Well, I haven't presented that before, but also the progression of chronic disease. Finally, the efficacy of the therapy if it were given. The same considerations for prognosis.

[Slide.]

What "endpoints" and tools should be used in clinical studies to determine performance for these indications? I put "endpoints" in quotes because I think it is another term that, at least it is confusing for me, and it gets tossed around a lot, but here are some examples.

One would be evidence of "recovery." Another would be evidence and kinetics of progression of HCV-associated disease. A third would be criteria for response to therapy.

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A really tough question is how long should these clinical studies last. One thing that is clear to people that work on hepatitis C and came out in the consensus conference at NIH last year, is that it probably takes a couple of decades to really determine what the long-term outcome of HCV infection is.

[Slide.]

Another type of consideration for monitoring chronic infection, how should rapidly changing concepts--this field is moving very fast--about pathogenesis and treatment of hepatitis C be incorporated into clinical study designs to support a product to come to market.

For those indications that pertain to antiviral therapy, which drugs, such as interferon and perhaps others, should be among the current inclusion criteria?

And as this field changes, how can the performance of an HCV-genome assay be extrapolated when we learn that there are genetic variances, such as genotypes, that were subsequently recognized to be important in the populations that FDA is relevant for considering, or for drugs that are subsequently recognized to be efficacious?

Should I present the questions now that we have covered far too much territory, go to these more general questions?

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What we will do is go through these quickly.

Is a two-step testing algorithm necessary when an assay is indicated for diagnosis of acute or chronic hepatitis C?

DR. THRUPP: Excuse me, John. For the panel members, are these in the handouts in the back of your slide packet?

DR. TICEHURST: I am pretty sure that these were in the material that were sent to the panel last Friday, and they are also in the agenda for today. The easiest way to find them is to look at today's agenda that has a white cover to it.

DR. THRUPP: And they are in the packet where all the slides were reproduced. That is the quickest way to find these questions.

DR. TICEHURST: I think I read the first question.

[Slide.]

The second question is: To establish performance of an anti-HCV assay, when indicated for diagnosis of acute or chronic hepatitis C, what criteria should be used to substantiate that studied patients have hepatitis C?

As an example of that, I forgot to mention this earlier, we have recently been asked to evaluate data where the way the data were presented to us, the specimens came

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either from patients who had acute hepatitis C, chronic hepatitis C, or were certified to be anti-HCV positive, and none of the information that supported those contentions were presented to us.

What performance criteria should be met by HCV RNA assays?

[Slide.]

To establish performance of a HCV genome assay for monitoring of acute or chronic infection, what monitoring indications should be considered and what endpoints and tools should be used?

Finally, are there any other combinations of assay and indication for which the panel would like to make recommendations, that something that you all feel is key that we haven't brought up?

There is a consideration that we would ask you to pay attention to, which is on the second slide. You are going to be seeing this slide several times today. These considerations come from the general questions that I discussed in the first session.

[Slide.]

We ask the panel, as it considers the answers to each of these virus-specific questions, to address several elements. Each of these elements pertains to the

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requirement in the FDA Modernization Act of 1997 for the least burdensome approach to determining safety and effectiveness.

These considerations are: Should we use, at CDRH, an approach that emphasizes very high analytical sensitivity, comparison of new and old assays with large numbers of specimens?

Again, keeping in mind that we don't have a lot of the controls available to the Center for Biologics at this point in time, and we don't have any laboratory capability at this point in time, are serially collected specimens necessary? Are new studies essential, and if they are essential, when should they be performed?

Thank you.

#### **Open Committee Discussion**

DR. THRUPP: We would ask the panel to address these questions that Dr. Ticehurst has listed.

Let's start with Question 1. Is a two-step testing algorithm necessary when an assay is indicated for diagnosis of acute or chronic hepatitis C?

Perhaps I could ask John one point for clarification. Are you referring to a clinical disease in this setting, not including early onset of infection before any clinical disease might be established?

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DR. TICEHURST: It could be all the above.

DR. THRUPP: The answers may or may not be the same for each.

DR. TICEHURST: We would appreciate your guidance for that.

DR. HOOFNAGLE: John, explain something to me. You used the term Class III device, and this goes to this question. I guess the FDA is in charge of screening blood and assays for screening blood, that is a very important charge, but here what I see you are asking about are diagnostic assays.

DR. TICEHURST: Correct.

DR. HOOFNAGLE: Can we separate these algorithms, these questions away from the blood screening issue?

DR. TICEHURST: That is a difficult question that our colleagues from the Center for Biologics have brought up. They are very concerned over the realm of hepatitis B and C, that of the possibility--they say it is a real public health concern--that no matter how carefully that assay kit was labeled to say in the biggest red letters, "Not intended for testing of donors of blood or blood products, only for diagnostic and monitoring indications," that in the heat of the moment when a reference lab was short on supplies or a lab was trying to cut costs, that they would use the assay

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for a blood donor.

There is also the concern that if one set up a system that ended up using a different algorithm for testing, that that could create further confusion in the laboratory field.

DR. HOOFNAGLE: I disagree with that. I think the blood banks can deal with these issues quite well, and realize that what they are doing is different than making a diagnosis. They are screening blood. They need tests that are very sensitive, but also very specific, so they have to go through all these funny algorithms, but in the diagnosis of hepatitis C, you don't have to do all that repeat testing, I hope. That is very expensive.

While I think the RIBA test, the strip test for verification of antibody is very important for blood banks, I don't think it is important for clinical diagnosis. I would use a completely different algorithm.

Now, this goes to the licensing. Someone said they didn't like regulations. Why should the FDA license any of these tests? Why? The reason is that it is important in patient decisions. If it is not important in patient decisions, you should leave the test alone.

An example would be quasispecies or genotyping, probably not important. Maybe you shouldn't get involved.

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But another area is they are very important, of course, because you are saying this patient has hepatitis A as opposed to having hepatitis B or hepatitis C, and what the doctor does and what the patient does then is very different.

But I would see that there should be two different classes of devices, those meant for the screening of our blood supply--and those people have been doing it for years, for 20 years, they know what is involved--and what you are trying to embark on here is develop license tests for diagnosis and also for monitoring therapy.

DR. TICEHURST: That is correct.

DR. HOOFNAGLE: Is that a reasonable approach to advice that the panel can give?

MS. POOLE: Yes. In fact, today, I am going to remind the panel that today's discussions are going to focus only for devices for diagnostic, and not for blood screening, because we don't have the CBER panel here present. We have the chairperson from the CBER panel is here, but we don't have a meeting of the CBER panel, so today's discussion will focus only on diagnostics and monitoring, but not for blood screening.

DR. HOOFNAGLE: Well, I would encourage that, that the algorithm for the diagnosis of hepatitis C should be

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different than what you showed us is used for blood banking.

DR. THRUPP: So, in essence, you are suggesting that the two-step algorithm is not necessary.

DR. HOOFNAGLE: You need two steps, but you don't need to repeat the EIA test unless there is something about it that puzzled them, like it was just at the cutoff or something, otherwise, I would go directly to a so-called confirmatory or supplemental test, and my bias would be for HCV RNA.

DR. THRUPP: Dr. Specter.

DR. SPECTER: I just want to follow up on that. In philosophy, I don't disagree with Dr. Hoofnagle. I would say, though, that firstoff, we talk here about safety and effectiveness. I think his comment is very important because cost-benefit is also a part of this.

The other thing is--and perhaps it is a patently obvious statement--but I think any decision has to be data driven, and the data has to be there to show that a one-step or elimination of the middle part of the first step is going to yield similar results, so that if the algorithm is going to change, a different algorithm must be compared to the standard algorithm to make sure that it is indeed effective.

I also would like to say that a one-step might be useful if, in fact, data-driven results show that at a

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certain cutoff level, if you get a positive, you are always going to get a positive in followup, so that that should be looked at, as well, in terms of whether there can be actually a single test above a certain level that is a positive.

DR. THRUPP: Dr. Hollinger.

DR. HOLLINGER: I would like to support what Jay has just said previously. Clinical disease is different than blood banking. When the prevalence is very low, as it is in blood banks, you are going to find a fair number of false positives. You can have a test that has got 99.8 percent specificity, and everybody is negative, there is always going to be 2 out of 1,000 that are going to come up positive.

That is not true in the clinical disease, and at least in my experience, most patients that come in or that patients are seen with an ALT abnormality, and that are anti-HCV positive, are invariably going to be HCV RNA positive.

The group that becomes a little more difficult are the patients who are anti-HCV positive and have normal enzymes. You would say, well, why do you test those. Well, part of the reason for that is because of looking into risk groups, people who have had transfusions prior to 1990, or

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even to 1992, when the second generation test became available in March for blood banks or high risk groups injection drug users in the past, and you might test them and find their ALT is negative, but their anti-HCV is positive.

It is in this group that the question of what to do becomes a little bit more important, and we are going to deal with this, but it has something to do with the relative degree of reactivity. I use this all the time.

If the sample comes back very high positive, a sample cutoff ratio of 2 or more in that regard, or the signal-cutoff ratio, however you want to space it, they are very likely to be HCV RNA positive.

We know that about 25 percent of patients over time will--or even from the beginning--will still retain their anti-HCV positivity and be HCV RNA negative, but you still need to find that out.

The ones that become questionable are the ones that have very low levels of reactivity as is true in the blood bank, with blood bank donors, and many of these will be HCV-RNA negative, and those patients that I will do a RIBA test in or an immunoblot test in--and that's about the only time--that I often will order an immunoblot test as a second step for trying to verify whether this is a false

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positive assay.

So, I think that a two-step is important, I think you do your anti-HCV initially, and it can be just a singlet, and then follow it, at least in my opinion, to follow it with an HCV-RNA, and when you get a negative on that, then, I would certainly follow it with a RIBA as just a practicality.

DR. THRUPP: Jay.

DR. HOOFNAGLE: Well, we can get rid of all the blood banking problems, let's throw them away. Then, I would say that you use these tests in three ways.

The first is diagnosis, and all you need is anti-HCV. The second use of these tests is monitoring patients, and there is where we get into the HCV RNA testing. To make the diagnosis, you don't have to test for HCV RNA by and large. It is a clinical diagnosis. But for monitoring, that could be a very valuable test.

The third use of these tests is for assessment of immunity. That doesn't relate to hepatitis C where we don't know anything about immunity, but for B and A it is very important. So, those are the three uses of these diagnostic tests. I think that keeping those in mind, you can focus on what kind of data you need to prove efficacy and safety and the stringency of the data.

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So, algorithm for diagnosis, for diagnosis only, I would say anti-HCV EIA, that makes the diagnosis. The two-step goes into the issue of then what do you do with the patient as far as monitoring.

DR. SPECTER: Or equivocal specimen.

DR. HOOFNAGLE: What I mean by that is you shouldn't send off a test and have the testing laboratory find a positive, and then immediately do HCV RNA because it's a part of their algorithm. That should go back to the physician to make the decision to do that test and to charge the patient, of course, for it.

DR. THRUPP: Dr. Charache.

DR. CHARACHE: I think that question of whether you need more than the anti-HCV is also in part population driven, and that is associated with the likelihood that you will get immuno-compromised patients in the mix, and certainly in our institution, for our particular patient population, we do have to follow it with a confirmatory test, which is either the RNA or r-nested PCR.

So, I think I certainly agree, and I think if it is a very titered one, you don't need to necessarily go further, but I think it will be driven by the patient base and sometimes the laboratory can be of assistance in your population-driven algorithms by an institution.

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DR. THRUPP: Two people have raised the issue of borderline or raising the bugaboo of equivocal ranges now. Does that mean that the primary algorithm should include a borderline or equivocal range where a two-step might be warranted or the HCV would be warranted even if it weren't for monitoring, but for primary diagnosis?

DR. HOLLINGER: Actually, I brought that up, and it is really a pet peeve of mine actually. You know, I can't perceive of getting a test back from a patient in which they tell me the potassium is positive, and I don't know if it's 3.5 or 5.5, or they tell me the albumin is normal, and I don't know if it's 3.5 or 5.

I can't see why we have difficulties, then, with giving back results for--and it just doesn't deal here with the hepatitis C test, it deals with all of them--a test that tells me how positive it is, and I always ask for it, and I have gotten our hospital now to give it to us as signal-to-cutoff ratios or cutoff-to-signal ratios, whatever, gives me a value of 1.0 and above being positive.

So, I can judge then if it's close to the cutoff level or high. I use that a great deal in separating out which are my problem patients, and usually these are the patients that are often referred to me in the same basis and the questions I get, and that is the first question I will

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ask the physician, I say go back and ask the laboratory what the cutoff value was, what the patient sample was, and then call me back and let's talk about whether we need to get some additional tests or do some repeats.

There are several rules that one uses, and either in large proficiency testing that we did with the HIV ACTG groups when we were proficiency testing some 50 labs throughout the country. We would often use as rules something either a three half or two-thirds rule or a 3/5ths or 5/3rds rule, basically meaning that the values would be between a two-thirds rule would be from 0.6 to 1.5 approximately, but it doesn't matter which rule you use or how you even do it. You don't even have to have a rule if you give me a number.

Then, I can certainly look at it, and if it's 1.5 times the cutoff level, I can say this is pretty close to cutoff level, it is very likely to be a false positive, or if it comes back 6 or 7, I don't care what the numbers are in there, I am not going to use them for anything clinically, so I don't really care if it's over 3, 4, 5, 6, or 7, but if it's between 1 and 2, or 1 to 1 1/2, or even less than that, that might be important for me and I might work with it.

So, I certainly think that this is something the

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FDA needs to consider in making recommendations to the manufacturer that they do provide these results as a number.

DR. THRUPP: You are saying I think two things. One, that there are out there a body of well-done clinical studies using an assay which has been well standardized to validate the significance of a borderline range, whether we call it equivocal or whatever.

Secondly, that definition of such a borderline range ought to be in the performance criteria, if you will, that the FDA is going to use in looking at new devices that would be compared with the predicate one.

Is that a fair summary? Dr. Specter had a comment.

DR. SPECTER: I am pretty much in agreement with the statement that was made. I do believe that perhaps I have less faith in those that I would consider less sophisticated than Dr. Hollinger in making those decisions and that I think a lot of bad decisions might be made if good guidance is not provided, so I think the critical thing is good guidance in that critical zone once whatever that zone is, is determined, is very important.

DR. THRUPP: That comes back to the importance of a package insert which includes that guidance which should be part of the approval process.

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Dr. Ticehurst had a clarification?

DR. TICEHURST: I want to make a couple points of clarification particularly in response to Dr. Hollinger's remarks.

We generally don't allow claims for numerical values that come out of assays that we traditionally regard as qualitative, and the reason for that is that the company has not demonstrated the value of a particular number that comes out of the assay was absorbance value or not. If you choose to do that, that is sort of your standard of practice.

The reason for equivocal zones, of course, is that the company has not been able to demonstrate acceptable reproducibility in a certain range of values above that range, above the equivocal range, it is reproducible, and then you can make a clinical interpretation from those results.

DR. THRUPP: You have two issues. You have analytical reproducibility in borderline ranges, and then you have clinical significance. I think Dr. Hollinger is saying that there is data out there that given an assay, which I am not sure if it is FDA approved as being reproducible, that there is data to assign clinical significance to it.

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Now, for new submissions, should we, the FDA, be asking for data on both aspects of this, as well as the clinical significance data.

DR. TICEHURST: It depends on the claims that the company wants to make, and I think we will have a chance to amplify this general area when we talk about quantitative assays for anti-HBs later.

DR. THRUPP: Dr. Charache.

DR. CHARACHE: As we go through these, I want to ask Dr. Ticehurst if he wants us to answer the same questions as they pertain to the physician office laboratory test that you mentioned you wanted us to consider.

DR. TICEHURST: Sure.

DR. CHARACHE: I wonder if I could ask my associates who have spoken so eloquently across the table if they would comment.

DR. HOLLINGER: You mean an office-based--

DR. CHARACHE: Apparently, there are some small devices which are being prepared for physician office labs, and the question is with such a device, might the panel recommend a different kind of supplemental testing than with the devices that we have had more experience with.

DR. HOOFNAGLE: We are very comfortable with the current EIAs because they have been through CBER and the

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blood bank experience, so there is enormous amounts of data on them. I would say with the little kits that you would run in your laboratory, that there probably should be another algorithm, which would be to go to the more rigorously licensed assays. I can't imagine a kit, though, in a doctor's office.

DR. THRUPP: Dr. Tuazon.

DR. TUAZON: Let me just ask a question as a clinician to both Dr. Hoofnagle and Hollinger. If a patient of mine comes in with abnormalities in liver enzymes, and the anti-HCV is positive, I really don't necessarily do the PCR unless I make a decision that I need to do this patient, right?

DR. HOOFNAGLE: So, again not separating the diagnosis.

DR. TUAZON: No, I mean if the patient is diagnosed and you talk to him and say there are therapies available, but if the patient does not want any therapy, you don't proceed. You do the assay because you want to monitor the response to therapy.

DR. HOOFNAGLE: Also, you say both acute and chronic hepatitis, I would say the serological test here will not separate those two, but that is an issue of time, so I hope you weren't trying to make that discrimination.

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There is this issue whether anti-HCV misses some patients either with acute disease because it's early, or chronic disease because they are immunosuppressed or something like that. That is very true, but they would be negative, so the two-step algorithm is useless.

So, all labeling of this test for diagnosis should have statements about false negatives, and based on the data that is presented to you recommendations to retest in a month or something like that, or if they are immunosuppressed, to consider HCV RNA testing.

DR. THRUPP: Ada.

DR. DeFOREST: I just have a quick question about the infant born to the high-risk mother who may or may not be known to be anti-HCV positive. What do you do in those situations and should that be addressed in a package insert, as well, that group of patients?

DR. HOLLINGER: Clearly, the infant is going to be anti-HCV positive if the mother is, since it is an IgG antibody and it is going to cross the placenta, and that can stay present for six months or perhaps even as long as nine months depending on the concentration of the antibody.

Clearly, in those cases, one couldn't use the anti-HCV tests for any diagnostic purposes, and one would then have to resort to HCV RNA if you really wanted to know

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that or you wait until 12 months or 15 months to do the test to see if that infant is positive, and that would probably be the most reasonable and cheapest thing to do in those cases unless the mother was extremely anxious and wanted to know that.

DR. DeFOREST: So the same pattern that we do with HIV now, we go directly to an HIV antigen.

DR. HOLLINGER: If you are really interested in whether the baby is infected, you would have to go to an HCV RNA test, and as Jay said, in the acute cases perhaps as many as 20 percent of patients who come in acutely will be anti-HCV negative, but their HCV RNA will be positive as it comes up very early in those individuals.

DR. THRUPP: Dr. Ng.

DR. NG: I am sorry, I have a separate issue to bring up if you wanted to finish the discussion about the infected infant.

DR. THRUPP: No. I was going to bring up another issue.

DR. NG: I would just like to question the panel here. I am a firm believer actually in following up the current algorithm. When you test a sample in singlet, there is still a human error issue involved, and if you get a positive, you still must question whether or not the

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specimen was pipetted out of the tube you thought it came out of.

So, that is why I actually favor doing a repeat in duplicate, and I favor moving on to an immunoblot assay because it is my understanding most of these assays use an antigen that is generated in a recombinant system. As such, they incorporate part of a bacterial protein, which a certain, very small subset of people will react giving you a false positive in the EIA.

So, I actually am in favor of the current algorithm for those reasons.

DR. THRUPP: Good points. It would be probably not a very good panel if we didn't have some disagreement on what recommendations should come down, but those are very good points.

Do Dr. Hoofnagle or Dr. Hollinger have any response to Dr. Ng?

DR. HOLLINGER: Well, no, there always can be tests, I mean problems in the laboratory, sample that is not that patient, and so on, but these tests don't miss a lot--if it is truly positive, they don't miss very many of the positives. A false negative test, in my experience anyway, is very unusual.

DR. THRUPP: How about in the immunosuppressed?

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DR. HOLLINGER: That is a different group. I am going to leave that out because absolutely, I mean if you have got an immunosuppressed patient, that is a different story and you have got to do something different, you need to know that. But outside of that issue, if this is an immunocompetent individual, the anti-HCV is generally going to be positive, will be strongly positive.

Now, it is going to come back to the clinician, and the clinician is going to look at that, and they are going to say it is positive, the patient has an elevated ALT, that is why many of us would do an HCV RNA at that point if it is negative, and at that point, I may come back and either do a RIBA or I would come back and say, well, you know, let me have this repeated, you know, maybe there was an error here and it wasn't really anti-HCV positive, but the clinician should be able to take care of that.

DR. THRUPP: Just to follow up on Dr. Ng's point, you are suggesting that we don't need to follow the same algorithm that is used for HIV, where the practice is still to do a repeat of the primary ELISA in the lab and then followed by a western blot. Because of the importance of the validity of the assay, I mean one could argue that hepatitis C is in the same category of chronic disease predictability and therefore the same degree of precision

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would be advocable.

DR. HOLLINGER: But we don't do that with a lot of tests in the lab that we get back, antimitochondrial antibodies, you know, for making decisions, and so on, and there is a lot of blood tests, even hepatitis tests, that are not done in duplicate afterwards.

From my standpoint and from my laboratory standpoint, we do it in singlet. We don't repeat it in duplicate unless there is a question about its level. If the reactivity is very low, we then will probably repeat it.

DR. SPECTER: I just want to follow up that comment because I think it is very important that what was just said is that good clinical practice is what is going to determine this, not regulation, because you are going to have circumstances where your result is obvious, you have got clinical diagnostic values, you have got enzyme levels, you have got negative values for other tests for other types of hepatitis, and if it looks like water and tastes like water and smells like water, it is water, and so at some point in time, you say one good positive test is sufficient.

A lot of what is going on in HIV testing has a lot of other factors going into it including history in which the tests in the beginning were a lot poorer, and so nothing has changed since the tests have improved in that regard

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plus the psychological circumstances are greater.

A good single positive test here is not a reason for second testing if everything else fits, and that is why regulation shouldn't drive this, but good clinical practice should.

DR. THRUPP: Maybe we could ask Dr. Ticehurst or Dr. Gutman, in the currently approved package insert, as far as directions for the application for HIV, is the repeat testing required or strongly recommended?

DR. TICEHURST: Since everything up until now has been licensed by the Center for Biologics, we have not approved any anti-HCV assays. I will ask Mr. Wilson to comment on that.

MR. WILSON: I am going to try to condense this. The repeat in duplicate approach, which occurs with all blood screens, when you get an initial reactive, was largely developed by the industry itself, because in hepatitis B surface antigen testing, if you had an initial reactive, the next step would be to do a confirmatory test. It was cheaper, more convenient, whatever, to do an extra screen, point one.

Point two, what happened is that there was a concern regarding, well, how many screens are enough. If it is still on the borderline, you could do duplicate and

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duplicate and duplicate, and what happened is that in the blood establishment situation, that is not tolerable because you could be potentially testing until you got the right answer or maybe the wrong answer. There had to be some type of a limit put on it.

So, what was basically developed was the approach was screen in singlet, if it is reactive, repeat in duplicate. If either of the duplicates are reactive, the donor is deferred, and then the algorithm of resolving whether or not the donor is infected is based on the ability to reenter the donor at a future date.

Does that help? All tests, HIV, HCV, HBsAg, all fall into the same anti-core, all the licensed tests.

DR. THRUPP: And the bottom line, of course, is that those are the directions for blood donor screening.

MR. WILSON: They are articulated in the package inserts and restated in the individual recommendation memoranda to blood establishments. Each test kit has a discrete recommendation memoranda to the blood establishments emphasizing about repeating, testing in duplicate, and what to do in the event of a repeat reactive, do the confirmatory testing, et cetera, what to tell the donor, what to do with the unit of blood, look back, et cetera.

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DR. THRUPP: But these issues have not been addressed for diagnosis.

DR. HOLLINGER: No, but clinical laboratories do follow those inserts. In general, now, when you send a specimen off, they are done almost the same way that the blood banks do.

DR. TICEHURST: I am not sure, Len, that I heard you say this, but it was my impression that if one were to go on to second-step testing, which at this point the only licensed version is the RIBA assay, that that second step is a recommendation, and not a requirement. Is that correct?

MR. WILSON: If one wants to reenter the donor, it would be viewed as a requirement. The issue at hand here with reentering donors is that if you have an altruistic donor who sooner or later, if you donate long enough, you are going to get a false positive somewhere--the stats are predictable to that--there has to be some mechanism by which to resolve that because, you know, just about every time of year, around Christmas, you know, we have blood shortages and things like that, and it is inappropriate to leave these people hanging.

DR. THRUPP: We have got to move on to other questions, but perhaps we could conclude this question by summarizing that there is not a unanimity of opinion on what

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should be recommended, however, perhaps we would all agree that a decision on this issue could be data driven hopefully and that if, as Dr. Specter mentioned, the position that there is a lot of data out there that replicability is indeed performance shown to be very good, at what level of errors one could argue about, but then one would not necessarily need to include the primary replicate testing.

DR. HOLLINGER: Dr. Thrupp, Dr. Teghtmeir and Dr. Holland maybe or some others from the blood banking community who see a lot of the tests, I would be interested if you specifically looked at samples that are, say, above a certain level, a cutoff level, signal the cutoff level, how often you found them to be positive in the singlet and then negative when they were done in duplicate in the repeat test. Do we have that data, Paul, or Gary?

DR. THRUPP: That is a good question. Could you respond to the microphone with that, please, sir. Give you name and affiliation.

DR. TEGHTMEIR: I am Gary Teghtmeir, Community Blood Center, Kansas City.

In answer to your question, Blaine, that data is present in blood center databases across the country, and it could be accessed to answer your question. I don't know the answer, though.

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MR. HOLLAND: I am Paul Holland from the Sacramento Blood Center in California. We have looked at it, and you can pick a number. I would say 3 of a serum-to-cutoff ratio, and I would say virtually 100 percent of the time the repeat tests will both be positive or both be above the cutoff. So, we do have huge amounts of data from millions of tests where we could give you such numbers or certainly ranges of numbers where you would have that certainty.

DR. THRUPP: So, it may well indeed be that a cutoff with a reliable ELISA could define an intermediate range that would require the replicate test and the algorithm. I see nodding heads. We don't have to vote on these, do we. So, we have got sort of a consensus.

Let's go on to the next question which Dr. Ticehurst has listed.

To establish performance of an anti-HCV assay, when indicated for diagnosis of acute or chronic hepatitis C, what criteria should be used to substantiate that studied patients have hepatitis C?

Dr. Hoofnagle, you look thoughtful.

DR. HOOFNAGLE: I guess there is two questions, but let's begin with No. 2. I think you need some other evidence besides your test itself that it's hepatitis C. I

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don't think this is a very difficult issue, acute hepatitis cases with antibody to hepatitis C that are PCR positive.

Where you get into difficulty are the patients who have chronic hepatitis C with normal liver enzymes and are PCR negative, do they have chronic hepatitis C and your PCR is no good, or have they actually recovered from hepatitis C and they have antibody left over.

Those are very interesting cases and very valuable cases, and I would encourage the FDA to create different cadres of types of patients, the typical acute, the typical chronic, the chronic case with normal enzymes, and then these patients who have normal enzymes and have anti-HCV, but who test PCR negative as a very special group to use in assessing tests.

Ideally, you would have a liver biopsy on them, as well, but that is really impractical and it may not be completely revealing. I think in very mild cases of hepatitis C, you might see something almost normal.

I am not sure that is a very satisfactory answer.

DR. THRUPP: You have suggested what we kind of brought up at the beginning, that the semantics do relate to clinical syndromes, and when we use the term "hepatitis," that implies that there is some abnormality from the infection, so our answer should be divided into two

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categories, those patients who do not have hepatitis as clinically defined by abnormal LFTs, which you have nicely summarized, in the chronic state, and there might also be the state following needlestick injuries in health care workers, for example, where that might also apply an algorithm, and that might be different from those with abnormal liver enzymes and hepatitis by clinical definition.

DR. SPECTER: I think you also have to consider the algorithm where you have superimposed upon that another hepatitis infection where you are going to have to worry about that, where all of the other clinical parameters are going to be confused by having, say, a hepatitis B chronic infection which could cause all the parameters you are seeing, and basically, in the absence of finding virus or viral nucleic acid there, you are not really going to know it's hepatitis C.

DR. THRUPP: I am not sure whether these responses answer your question, John. Do you want more detail?

DR. TICEHURST: No, I thought that it was quite appropriate. If you recall, I listed some possible criteria, and I think the discussion I have heard is that that is basically in agreement with those criteria.

DR. THRUPP: The Question 3, that you have selected out: What performance criteria should be met by

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HCV RNA assays?

DR. HOOFNAGLE: This is really a very big question, and it also goes to the use of HCV RNA as a diagnostic test as opposed to a way to monitor patients.

I think it can be used as a diagnostic test, but really should be reserved for special situations, and most of them have come up so far, for instance, a child born to a mother with antibody or the person who has had a needlestick accident and you test them a week later, two weeks later, you might want to use HCV RNA.

We are not really talking about diagnosis, we are talking about very special situations, of patient with immunodeficiency, agammaglobulinemics, for instance, and so forth.

So, I don't think the test really should be sold as a diagnostic assay, but rather as a monitoring assay that you can use for diagnosis in very special situations, but in situations where monitoring is important, so that what is the importance of diagnosing a child born to an antibody-positive mother at three months of age unless you intend to do something like treat the child or isolate the child or something, so I think it really puts it into the category of monitoring.

What performance criteria? I think we can go

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through a lot that the FDA themselves could do, but really it has to do with sensitivity is the key in HCV RNA testing, not specificity. Specificity is the bugaboo of PCRs, and there is no cure for it. I mean that is why you can't use that assay as a screening assay I don't think, has been my experience. It has to be used as a monitoring assay in someone you highly suspect of having hepatitis C, and then the importance is sensitivity and reproducibility, can the assay, not only is it sensitive down to, let's say, 1,000 genomes per mL, but also, can the assay be used in the field by your local testing laboratory or will they make errors and make it useless.

This was an important issue in the early days of hepatitis B testing, where there were so-called second-generation tests that were pretty good, but when they were performed in the field, they were awful. People were not very good at doing the test, and when we went out and inspected these places, we found there is no use blaming them, these tests just don't perform well in the field, and that is what I would be concerned about these tests, as well.

So, the two issues I would be concerned with is sensitivity and whether they can be used in the field well. So, it is not just your company doing the test, your

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Chirons, or your Roches, but your local laboratories performing that assay.

As far as the level of sensitivity, I think you need to hear data. I hear bandied around 100 genomes per mL or 1,000 genomes per mL, and it depends on their standards. This is where I think the FDA would be helped a lot by developing a panel of standards for HCV RNA at different levels, different genotypes to assess new assays for HCV RNA. I don't think there is any way around to developing such a panel that you could use.

DR. THRUPP: Mr. Wilson.

MR. WILSON: FYI, CBER is in the process of developing an HCV RNA panel, but it is targeted at blood screening assays, so the first step is at least being taken.

DR. THRUPP: Dr. Charache.

DR. CHARACHE: Concurring with Dr. Hoofnagle, I think we should have performance standards, as well, though for that subset of patients for which it is appropriate to use a molecular detection test for diagnosis. So, I think there I would question what any special requirements might be in terms of the source of the specimen.

I think the issue of sensitivity and quantitation clearly comes in if you want to measure very early after the infection or later in the chronic state in which the limits

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may be less secure, and I think that any package insert, the labeling should include the cautions appropriate to the use of such a test for diagnostics, as well as for monitoring, because it will be used for both.

DR. THRUPP: Do you suspect that it will be feasible to develop enough, let's say, for a manufacturer to produce enough data in those subsets that would be meaningful in numbers enough to provide statistical guidelines or should be the FDA attempt to seek data sets in these special subsets?

DR. CHARACHE: I was very careful not to specify what I thought those performance standards ought to be, because I have not prejudged in my own mind whether they have to come from that patient group or whether one could use surrogate markers that would apply to that patient groups.

I certainly agree that some of those patients would be difficult to come by as a population in its own right, but on the other hand, certainly we have urban centers--I won't volunteer any particular center--but in which it would not be difficult to get a moderate number of people who fit that category.

DR. THRUPP: Jay.

DR. HOOFNAGLE: This goes a little bit to are

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serial collected specimens necessary. I think they are nice and they are wonderful to show the serologies of the various forms of hepatitis, but as far as licensing tests, I don't think they are very necessary tests for diagnosis.

The serial collected specimens that are necessary would be those of patients with acute hepatitis, not the typical blood transfusion recipient where you have serial bleedings. Those are very valuable, but those are artificial situations that physicians who are dealing with diagnosis don't deal with.

I think you need a panel of specimens that someone like Dr. Thiele could come up with, of people presenting to their hospital with acute hepatitis, and then a specimen from them a month later and two months later if you need seroconversion panels just to basically show what percentage are positive to begin with and does it help to test later on, do you pick up any more rather than the serial specimens after someone exposed, which are very critical.

I think the same goes for PCR. There, the serial specimens can be provided through studies of therapy, which really present a challenge to PCR tests because the levels of virus fall, and they can fall below the level of sensitivity quite clearly, so those are easily obtained panels.

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So, coming back to this issue of serial collecting specimens, I don't think you need to go back to the old days of tests like after blood a transfusion picking up serology.

DR. THRUPP: Dr. Specter.

DR. SPECTER: I would like to comment on that because I think there are certain standards where they are important in terms of a test verification, and that would be, for example, where you have a test where you are seeing a number of so-called false positives in early specimens, which actually turn out to be just a more sensitive test that is picking up reactivity sooner, and this could verify that that, in fact, is not a false positive because subsequent testing in serial specimens would verify it.

That is one circumstance. The other, you actually already alluded to, and that is in drug testing to verify that, in fact, if you follow, you can show that a particular test is valuable in following a patient's prognosis following therapy.

I think serial testing has a value, but there are limited circumstances where that value is.

DR. THRUPP: Blaine.

DR. HOLLINGER: I guess part of it comes down to whether you can get the same information from dilutional studies, endpoint dilutions, and so on. I understand there

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are differences in acute disease with avidity of antibody, with combinations of IgM and IgG that might be present in the samples, and so on, but by and large, I have not found that to be a real major problem that cannot be resolved usually by dilutional evaluation of sensitivity of an assay.

I suspect there may be some that might be detected in an acute specimen that would have nothing to do with dilution, but I still think that you could do most of this by just having a good panel and having it span the links. You don't really care about the high levels, who cares what the upper levels are necessarily, but you certainly want to know down near the cutoff level how well the laboratories can do.

DR. THRUPP: Are you suggesting that as part of a validation package that a manufacturer would have to produce that they would include dilution studies on positive specimens?

DR. HOLLINGER: I think specimens, either where they are producing them or whether panels are provided by the FDA or other places, proficiency panels, and so forth, they clearly need to include low concentrations of either HCV RNA or antibody.

DR. THRUPP: Dr. Charache.

DR. CHARACHE: I wonder if this question might not

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be better data driven as it applies to a given format or a given new test. I mean I can certainly see some IgM issues here. We are thinking in terms of what it says now, but if we are going to project further into the future, I think that it might be reasonable to want to see enough serially collected specimens maybe purchased, not a large bank of them, but just enough to show that the dilutional studies would be valid.

DR. HOLLINGER: Seroconverting panels are always wonderful things to have, but they are really difficult to obtain. I think probably the FDA and other have this information available. It would be interesting to me. I will bet you that the most sensitive assays will probably pick up in a test in which, say, an antibody becomes positive at the very early stages or p24 antigen when you are looking at the HIV assays.

My perception would be that if they were detected at that level, it has something to do with the sensitivity of their assay and that a dilutional study would probably have demonstrated as well, and that would be a question I would place before the FDA if that has been the case. That data probably is available.

DR. CHARACHE: That would be data driven then.

DR. TICEHURST: May I make a point of

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clarification, please?

DR. THRUPP: Yes.

DR. TICEHURST: One of the points that Tom Simms mentioned this morning is at this center, at this point in time, we don't have the laboratory resources to develop the kinds of panels that are being suggested. I see those kind of panels as being an enormous benefit to everybody if they existed, but we don't have those resources.

Some such resources are at the Center for Biologics, and Mr. Wilson can clarify that if he wants. I know there have been some efforts in some of this work at the Center for Disease Control and Prevention, and I would ask the panel perhaps to consider what types of resources this center might direct if they feel it is an important goal.

DR. HOOFNAGLE: Well, your division might consider a contractual arrangement with a group to do the testing for you. That would be one thing, to gather samples and just be a surveillance system, and something like that. I think that is a very reasonable approach, and then you don't need a laboratory, and then you can turn off the contract anytime you don't want it anymore. That, I think is a very good mechanism and might be something you could recommend to your people that would be helpful, to have a contract with a

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group that would assess these tests, collect panels. We have some people in the audience that would like to take that contract, I am sure, and that you could monitor.

That is what was done in the old days with hepatitis B.

DR. THRUPP: We had better move on to the next question which has been put on the screen.

To establish performance of a HCV genome assay for monitoring of acute or chronic infection, what monitoring indications should be considered and what endpoints and tools should be used?

We did hear, I think maybe Jay and maybe Blaine suggest that at this point in time, the clinical data to make it a conclusion that you need to do the genome assays may not be before us.

On the other hand, there is data being derived in studies everywhere, and in the next two or three years, the FDA may be faced with evaluating additional clinical data that may or may not suggest clinical significance for these assays, so I think we have to come up with some suggestions for the FDA.

Who wants to respond to this again?

DR. HOOFNAGLE: You could begin with the NIH Consensus Conference, what they recommended as far as HCV

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RNA, which they did with some timidity because the tests are licensed, but they stated that before therapy of hepatitis C, you should test the patient to show that they are positive and that it is appropriate to test them, they recommend at three months during treatment to see that the treatment is working and to use it in followup to show that the treatment has resulted in a response, a sustained response.

So, I would recommend that you go with an outside group that is giving you some recommendations about when and how this test is needed. I think there are a couple other indications for the use of a test that might be mentioned and assessed.

One is the immunosuppressed agammaglobulinemic patient, the transplant situations, the HIV positive patients, and the child born to an anti-HCV positive mother.

DR. THRUPP: Dr. Hollinger.

DR. HOLLINGER: In addition, as has been mentioned, you have heard this several times today, it is the most sensitive tests that are the most important, particularly in monitoring patients.

We know that if patients are positive at a certain stage or even at the end that they are either relapsed or they are not really cured. If they are negative, they may

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or may not have a sustained response, but at least they are negative to start with, and that level has to be quite low.

Now, whether it's a qualitative or quantitative test it doesn't matter. If I can get a quantitative test that is equally sensitive to the most sensitive test, I will take a quantitative test anytime, but if the qualitative test is more sensitive, what I would want is a test that is very sensitive.

Now, whether that level is set at less than 1,000, which is probably a reasonable starting point, or less than 500, or less than 100, that is another issue, but there is probably a certain minimal level that each test ought to meet, and I guess I would set something initially at less than 1,000 right now copies per mL as a starting point.

DR. THRUPP: Perhaps my comments were not quite on the mark. You are not referring to genome typing here. You are merely referring to a molecular quantifiable test, and you are talking about the genome assay, or are you talking about the high sensitivity PCR, for example?

DR. TICEHURST: The HCV genome in quotes refers to any state of the genome in a patient any way it can be measured, but I think the comments we are getting with regard to assays just for detecting HCV RNA presumably we are referring to serum and plasma are very helpful.

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The problem that I am not yet hearing a response to yet is I understand the indications, but the tough issue we have to deal with is having a manufacturer show that the assay is doing what they say that it is doing.

There is a spectrum in there. One of the spectrum is what Dr. Hollinger just referred to, demonstrating--and with what Dr. Hoofnagle said--demonstrating with a panel of well-characterized material standards that they can analytically detect a certain amount of HCV RNA.

You can go to the opposite end of the spectrum, is to get involved in studies that will go on for the next two or three decades to determine that a certain HCV RNA concentration of a certain presence of absence of HCV RNA detected in a patient now means something for that patient 15 years from now.

It is my opinion--I don't think anybody will disagree--we can't keep these assays off the market pending the results of such studies. What kinds of studies are appropriate is the real question.

DR. THRUPP: Any other response? Jay.

DR. HOOFNAGLE: Dr. Ticehurst is really caught in a conundrum because what Blaine and I are saying is these tests are the gold standard, and you are saying what gold standard should we use, and we are saying these tests

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are--you know, and we don't have any other gold standard, because there is nothing more sensitive.

Our general findings--and I think you need the data presented to you on this, not just us saying it--is that HCV RNA testing by a good PCR is the best that you can achieve. If you are negative after stopping therapy for six months, that is the best evidence that the patient is cured.

The ALT, liver biopsies are not as good as just being PCR negative, but of course, you have to go and have them show you the same data, and you are going to ask us why did we say that, and we said that because long-term followup on patients treated, and I guess those are the panels that would be most valuable for them to test, six months after therapy with interferon, if they are PCR negative, they remain in remission, and if they are PCR positive, a high percentage of them continue to have evidence of chronic hepatitis.

I think that would be kind of the best establishment of performance that the test means something that has become negative. I think you should also ask them to show that among 100 or 200 or 1,000 patients with chronic hepatitis C, that 95-plus are positive by their PCR every time you test them, some cutoff.

For instance, in our trials of interferon,

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virtually 100 percent of patients are PCR positive when they started therapy, and these were done before PCRs were available, so that type of criteria is not hard to come up with. A very high percentage of patients with chronic hepatitis C should be PCR positive.

DR. ZABRANSKY: I have a couple of questions concerning the qualitative versus the quantitative tests. Do we really need a quantitative test if the qualitative tests is sensitive enough, as you indicated, except for following or trying to develop new therapeutic modalities?

Would not the qualitative test be sufficient then for following a patient if it was sensitive enough?

DR. HOLLINGER: Yes, I would say it probably is. Where the quantitative test has some potential benefits is we know as a group, patients with high concentrations of virus are less responsive to therapy than those with lower concentrations, but looking at the individual patient, you can't say if that patient is going to be that, so it really has not very much relevance.

The patient may want to have that information if he is trying to decide what the possibilities are for--it is just like the genotype, it is just another issue also. There are genotypes that are very sensitive and several which are resistant like one in four.

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So, the patient may want to have that information to decide that, but patients who are genotype I get cured, and patients with genotype II and III don't, so that is an issue, but in terms of the quantitation, I will tell you where I see it has maybe some benefit.

Jay has mentioned about the three-month rule which was mentioned at the NIH, which essentially states that if the ALT is normal, and the HCV RNA is negative, then, one would continue on with therapy. If both of them are positive, then, you might stop therapy at that time. I think that is a correct assumption.

But the issue is if I had a patient who started out with 30 million or 20 million copies per mL, the median is around 1 to 5 million, say, around 3 million, but if I started out with somebody with 10 or 15 million, and three months later that person is down to 10,000 or 5,000, that is still positive in a qualitative test. I don't know where he is.

I might then decide that this is worth going on and continuing treatment in that patient, so that is where the quantitation may have some benefit to me, but as I said if it comes down to cost and the test is not as sensitive, then, I certainly would go with the most sensitive test available.

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DR. HOOFNAGLE: For the HIV people in the room, not the positive people, the people who are experts in HIV, quantitation in hepatitis C has not been as dramatically correlated with outcome than in HIV, in fact, it has been frustratingly lack of correlation of titer of virus and severity and outcome, but it is still from a research point of view, such a valuable test, and provides such information, and with the development of new therapies, it may be absolutely critical.

If we have protease inhibitors, they are not going to make the test negative. They are going to drop it by a certain amount, and so you will want to assess the relative potency of antiviral agents using these quantitative tests, they will be essential, but these are research uses of these tests.

I think at the present time if you want to put your efforts somewhere, you should go with the qualitative tests, but I think the quantitative tests may ultimately be very important and somehow we need to encourage industry to press forward with making these tests more reliable and better.

That is again another level of regulation, as I see it, the highest level being for the blood bank screening test, extremely rigorous sensitivity and specificity. The

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second level is these diagnostic tests. It is important to show that they are good.

A third level is these research assays, and I don't know how this agency will deal with those. I suspect that you should leave them alone until they are needed in clinical medicine.

DR. HOLLINGER: There has probably not been a disease for a long time where there is so many unapproved tests out there being used as a gold standard.

[Laughter.]

DR. HOLLINGER: I think the key is what we would like, if you want to look at it, is I would like to be sure that if I say, look, we are doing our tests mostly in our lab here, but even in our lab, I would like to be sure that if a test was sent off somewhere, to a company that is going another test, a commercial test or even an in-house test, I would like to know how good they are, I want to know what their precision is, what their coefficient of variance is, and how well they are, can they really detect copy numbers that I am concerned with.

That is what I want to know, and I want to know how often they can do that without an error, false negatives or false positives, and things like this. So, panels out to those individuals or to those particular places to have done

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is very critical to me.

I mean we are already using these tests and making decisions based upon them, but if we had that kind of proficiency testing, whether it is CAP-gearred or one of the other organizations, it doesn't matter, I would certainly like to see that kind of evaluation done with the tests in the laboratory.

The kits are good, it is often the laboratories which are not good, so you really--often it is more evaluations of laboratories and technicians and personnel than it is of the kit itself.

DR. THRUPP: You just made a little bit of a non sequitur. You asked for validation of these assays that are being used even for the research protocols, and then you said, well, the kits are good, but how do we know the kits are good or how is the FDA supposed to know that they are good aside from performance, proficiency checking in the lab?

DR. HOOFNAGLE: Well that is not the FDA's business, that is the other group that I love so much called CLIA. They knocked me out of this testing entirely. In fact, I don't do these tests anymore, I am afraid to.

But this goes to the issue that if you are going to license a test, they are going to have to demonstrate

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that in the field, it can be done reliably, and that goes to what Blaine said. If you have a test that in the field doesn't do very well, I think you need to reconsider whether it should be an FDA-licensed assay.

DR. THRUPP: Could I ask one other simplistic question. Several comments have been made about the importance of having panels of selected, especially sequential sampling from patients and having defined levels in standard samples.

Are there good data--and I assume there are--data that would establish on the stored standard panels that they are replicable and reproducible over months, years, sometimes decades of storage?

DR. TICEHURST: Can I answer that, am I allowed? I think there are sort of two questions here. One is there is a couple of studies in the scientific literature that come from the European hepatitis study group, so-called Euro-Hep group. Zaiijer is the first author in those two studies. One came out in '92 and the other in '96, I think.

The bottom line in that was that the assays that were being used, some of which were commercially available and some of which were--this is all for HCV RNA--some of which were home brew assays, there was terrible reproducibility from lab to lab, and the ability of the

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different labs and/or the different assays, it is hard to pick them out, to discriminate one from the other was very bad.

With regard to your other question, there was another part to your question about storage and panels, what I am aware of is that the data that exist for the stability of HCV RNA, it is very important to separate the serum or the plasma from the blood specimen within hours. That is I think a fairly constant finding.

As to how well the RNA persists over time, that is a tough question, but I think anybody in the room who has worked with RNA knows it is a very unstable molecule no matter what package it is in.

DR. HOLLINGER: John just brings up a very important question, is the processing of the sample, collection and processing of the sample is critical for PCR testing.

We know that EDTA or ACD, but probably EDTA is superior to serum. You could lose almost 30 to 50 percent of your RNA in serum. It doesn't really make a lot of difference. You could have 10 million copies per mL and you lose half of it, so what, the test is still going to detect it, and so it doesn't matter, and most of it is quite high.

DR. THRUPP: Most of it is put on drug

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"panaceamycin" that looks like it was 50 percent active.

DR. HOLLINGER: That's right. I forgot where I was now.

DR. DeFOREST: You were stressing specimen processing.

DR. HOLLINGER: The specimen processing, I don't know if that is under the purview of the FDA or the manufacturer, but as I said, it is a critical thing.

Again, the samples that sit on the clot lose rapidly, lose detection of the genome, and so it must be separated within a very short period of time, perhaps two to six hours, how if it is stored, if it is tested within 24 hours or more, then, that's fine, otherwise, it should be stored perhaps at minus 70 degrees.

We know at 20 degrees or 30 degrees for long periods of time, there is a perception that the concentration, at least the copy number seems to go down, and all of these things are very critical to do that.

Now, there are other tubes out there in which separation is excellent, the serum separator tubes and stuff like this are probably useful. The main thing is getting it away from the clot. I do think that is an issue that really needs to be dealt with in the inserts about how the sample is collected.

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DR. THRUPP: I think we have better break for lunch. We are already late. Maybe we can eat a little more rapidly and try to get back on time.

Thank you.

[Whereupon, at 12:50 p.m., the proceedings were recessed, to be resumed at 1:50 p.m.]

AFTERNOON PROCEEDINGS

[1:50 p.m.]

DR. THRUPP: Let's reconvene and move right along in the agenda to our ABC's today. We are going CBA. Now, if Dr. Ticehurst could introduce us to hepatitis B.

**FDA Presentation**

**Hepatitis B**

DR. TICEHURST: We are going to talk about hepatitis B. I am glad that, after having lunch, I get to stand and talk rather than sit and try and stay awake.

[Slide.]

The first example that we would like to discuss, in terms of general issues, are assays for IgM anti-HBc. I think a number of the considerations here apply to some of the discussion earlier today about serially collected specimens.

The first point, and this is amplifying one, no pun intended, that Tom Simms mentioned this morning that the key--one of the things he said this morning is that all assays are not created equally. One point I want to reemphasize for the panel is that we are not talking about the assays that have already been approved. We are talking about assays that we are being asked to evaluate for approval.

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All assays are not created equally. One of the traditional criteria for a Class III device into which category all of the assays we are talking today fall is that they need to stand on their own. They need to show what they are doing, what they say they--I think I am in the post-prandial situation, too.

They need to prove, to some extent, that they are doing what they say they are going to do.

Variables in assays are particularly true for assays that detect IgM antibodies. I recall, years ago, when I first started working in the laboratory and was using some of the reagents from an IgM anti-HAV kit, it struck me very strangely when I read the package insert that, for doing that assay, the sera were to be diluted 1 to 4,000-fold. I thought why is that.

I gradually deduced, and it was subsequently confirmed for me by the manufacturer that the purpose of that was so that the IgM assay would become a good marker, a reliable marker, for detecting acute or recent infection which is the purpose of most IgM assays.

The reason that dilution was chosen by the manufacturer was so that the assay would have high predictive value, positive results would have high predictive value, during that period of acute infection down

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to what we usually assume to be four to six months.

But one of the points I am making is, at least up until now, we can't assume that each new assay for an IgM assay is going to perform that way.

The other issue, with regard to the particular issue for the IgM anti-core assay is that their performance is also affected by the recognized high frequency of positive results during exacerbations of chronic HBV infection. So both these factors, then, complicate interpretation of results from IgM anti-core assays which are indicated, in the case of an HBsAg-positive patient for distinguishing acute from chronic infection.

They are also indicated, as was alluded to this morning, in the very early period for diagnosis of acute infection before there are detectable levels of HBsAg.

But, obviously, we have a problem here. We want to be able to tell a physician for a particular assay what a positive result means. If, for a particular assay, you get a positive result from somebody with a chronic infection, that is not helping the physician at all.

[Slide.]

With regard to IgM anti-core, is it appropriate to test serially collected sera to establish the temporal patterns of new assay results? This goes back to one of the

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general questions I brought up this morning, why would you do such testing.

Well, for one thing, they could be--and this is something that Dr. Specter and others talked about this morning for C--used to detect conversion from anti-core negative to positive during the early phases of acute infection, which would be a determinant of clinical sensitivity.

Likewise, by looking at serially collected specimens, you could have a determinant of clinical specificity where early during infection when IgM anti-core might be the only detectable analyte, the results from later collected specimens would confirm the specificity of that result.

In addition, late during acute infection, as the levels of IgM anti-core wane, it would be useful to know how a particular assay is converting from positive to negative as a determinant of clinical specificity, again with the point of view of if a result comes back positive for a particular assay, how long can we expect it to be positive after the acute infection.

Finally, with regard to this particular marker, how often positive results occurred during exacerbations of chronic B.

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[Slide.]

Alternatively, is there a reference assay to which a new assay could be directly compared by testing a single specimen from each patient?

Could an unapproved assay for HBV DNA--and as I mentioned this morning, there are no approved assays for HBV DNA--be used as a criterion or the criterion for determining the specificity of IgM anti-core positive results for sera collected during the early phase of infection?

[Slide.]

General issues with regard to assays for HBV DNA. What indications are appropriate? It has become very well recognized--and I think Dr. Hoofnagle has pointed this out in a number of things that he has written--that recognized formats for these assays can greatly affect performance characteristics.

The concentrations of HBV DNA are generally high enough or are often high enough that they can be detected without amplification either by direct hybridization or by hybridization with signal amplification, or by using enzyme immunoassays wherein the analyte, the DNA that is being detected is hybridized to another nucleic acid, usually an RNA, and then those hybrids are detected by antibodies to the DNA RNA hybrid.

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Of course HBV DNA can be detected after amplification either qualitatively or quantitatively.

[Slide.]

Without going back over all the general issues that we discussed about HCV RNA, one of the questions is are there any different considerations that apply to assays for HBV DNA?

We developed an impression, and I am wondering if it is correct, that to date the genetic variance that had been recognized for HBV don't seem to have the same impact on HBV DNA assays to the same extent that HCV RNA may be affected, and genotypes being an example.

[Slide.]

Another general issue is assays for anti-HBs. Dr. Hollinger, this directly deals with your pet peeve that you brought up this morning. I am sorry, the first one doesn't necessarily, the second one does.

What are the indications for a qualitative assay that reproducibly detects less than 10 IU/L of anti-HBs. 10 IU/L is the accepted criterion for immunity to HBV. Many of the assays that currently are out there will detect much less than 10 IU/L, but they usually include a calibrator that allows one to indicate when a certain result is qualitatively more than 10 IU/L.

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The question we have is why not have the cutoff reproducibly around 10 IU/L, is there any clinical utility to be able to detect less than that.

This addresses Dr. Hollinger's concern. There are not any commercially available quantitative assays for anti-HBs in the U.S.A., and in addition to the material that was sent to panel, Mr. Wilson pointed out to me that CBER--and he did say this morning CBER does regulate essentially what are calibrators for quantifying anti-HBs, again for the purpose of looking at hepatitis B immune globulin.

But what are the indications that are recognized for quantitative detection and what types of clinical studies should be performed to determine the performance of a quantitative anti-HBs assay?

[Slide.]

The next general issue has to do with new studies for HBV-specific markers. What I have done here is highlighted--I have taken basically the same considerations that we talked about for HCV RNA assays and highlighted those things that were different or that might be different with regard to hepatitis B versus HCV, but I will just read through it.

How should changing concepts--maybe not as rapid

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as for HCV--about pathogenesis, treatment, and prevention--as Dr. Hoofnagle mentioned, there are well accepted vaccines against hepatitis B--be incorporated into clinical study designs, what drug therapies should be among current inclusion criteria, and how can we extrapolate the performance of HBV-specific assays as we learn more either with regard to newly recognized genetic variance, newly-efficacious drugs or any changes in vaccine recommendations that might occur.

[Slide.]

For which analytes--keep in mind here we have at least 7 for HBV, the 6 commonly recognized serologic markers in HBV DNA--and which indications are new studies essential?

If new studies are essential, what types of new studies should be performed before an assay is considered for approval, and which could be performed in the postmarket arena?

[Slide.]

Now a couple of examples of indications. One would be monitoring chronic HBV infections. Again, a lot of the considerations I am bringing up here are similar to what we discussed for HCV this morning.

It is a little different, though. Current monitoring tools include the serologic markers for HBV, the

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corresponding antigens and antibodies for the surface e, and anti-e, and HBV DNA, and the other tools are like those that we have described this morning for HCV.

[Slide.]

The monitoring indications could include basically all the same types of indications we mentioned for HCV with the exception, with these different serologic markers, they can be followed also, and the question of course is how should new assays be characterized to determine their performance with regard to these patterns.

What I have done here is sort of a sequential list of a typical sequence of changes in analytes as a patient recovers from chronic hepatitis B, and a lot of this comes from work that Dr. Hoofnagle and others have done.

Typically, the e antigen converts from positive to negative followed by appearance of antibody to e antigen. The disappearance of HBV DNA depends on how sensitive the assay is. I have put "disappearance" in quotes because my concept, maybe it is naive, is that once one is at least chronically infected with HBV, you have got it in your liver, liver DNA from then on.

Finally, if a patient fully recovers, they go first from HBsAg-positive to negative, and then develop anti-HBs. I put those in parentheses because a lot of

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patients--my understanding is a lot of patients never make it to that point.

[Slide.]

The prognosis and efficacy considerations would be like those for HCV infection. The other questions come up again, like HCV, what endpoints and tools should be used to determine performance for these indications? How long should these clinical studies last?

I have an overhead that I need to just quickly check that I made this morning. Bear with me just a second.

A little shorter than the discussion for C, we will now come to questions for HBV.

My things keep disappearing today. I don't know what happened to that single slide, but you will remember the slide that dealt with the general considerations that would apply to discussion of these questions.

I will read them off.

What types of studies are necessary to establish the performance of assays for IgM anti-core or for HBV DNA?

Are there recognized indications for using a quantitative assay for anti-HBs, and if so, what types of studies are necessary to determine a new assay's performance?

In clinical studies, for establishing performance

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of HBV-specific assays for monitoring chronic hepatitis B, the same questions as we had for C.

Are there other combinations of assay and indication for which the panel would like to make recommendations?

Another thing to consider here was with regard to B, which is one that has come up a lot, is that many of the assays for the HBV analytes, in different forms, many of them have been out for 20 years, so in a sense, they should be well understood. On the other hand, there are no reference assays that we are aware of for any of these markers.

I think that is all I wanted to say. Thank you.

#### **Open Committee Discussion**

DR. THRUPP: Let's leave the slides on.

We can start by addressing Question 1.

Are there any general questions before we get to the specific that any panel member would like to ask Dr. Ticehurst?

DR. CHARACHE: Again, these are generics, so these questions are to be applied to all kinds of test that are not already on the market, regardless of what they are looking for, unless it is specific for nucleic acids, and regardless of the format, whether it's a doctor's office or

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a sophisticated reference laboratory.

DR. TICEHURST: The answer is yes. We are not asking about how to use assays that are currently approved. We are asking what types of claims a manufacturer might make for different types of assays, and then what is appropriate, especially in terms of clinical studies, for generating the data for them to earn approval in all the scenarios you mentioned.

DR. HOLLINGER: John, you brought up some very good points in the assays. We know that if you have a proper test, a test that can detect IgM anti-HBc at very low levels, that most chronic hepatitis B patients have low levels of IgM HBc circulating, and it is during those periods of exacerbation and reactivation of their disease that perhaps 15 to 25 percent--Jay, you may have a better number--but I think somewhere around 15 to 25 percent will become IgM anti-HBc positive, but again at a very low level, as distinct from somebody who has an acute disease in which their signal-to-cutoff level is markedly different.

Now, one of the reasons, you mentioned the fact that they tried to get away from this by diluting the samples, in some tests it's 1 to 1,000, in other tests, it's 1 to 4,000 or 2,000, various dilutions based on the test.

The other reason that they did that also is

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because below about 1 to 100 dilution you get a prozone, and even very positive samples in acute disease will be negative. So, that was the other reason they couldn't go down to 1 to 100, 1 to 10, things like this, because you miss then the acute disease you are looking for.

So, I think with any assay that comes up, one has to sort of deal with these issues because it is a very useful test for distinguishing acute from chronic disease except, as I said, you get into that sort of gray zone now in reactivation of chronic hepatitis B, but still it works quite well and should always be considered as the principal test for distinguishing these two.

You also mentioned one thing which I wasn't sure of. I have never seen an IgM anti-HBc which was the only detectable analyte, I have just never seen that. Almost invariably, HBs antigen comes up, is the first thing that comes up in an acute infection. That is before the patient gets ill.

The IgM then comes up later. The only time you don't see the HBs antigen around is during the window period, but then their anti-HBe or another marker, certainly their total anti-HBc is positive at that time, as it is all the time in addition, but I have not seen the other one where it is the only analyte, so I don't think that is

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really a particular problem, particularly in clinical disease.

DR. THRUPP: Dr. Hollinger is addressing, of course, specifically Question No. 1, Part A, studies necessary for establishing performance of IgM anti-HBc.

I would suggest that when we are considering performance in this context, you are wanting a response both from the standpoint of analytical performance, as well as clinical indications and validity of indications.

DR. TICEHURST: The focus of the meeting today is on clinical performance, but I think as we got in the discussion of HCV RNA this morning, there are certain analytical criteria that may be clinically pertinent. So, I would say the analytical discussion should only pertain to clinically significant thresholds.

DR. THRUPP: Dr. Hoofnagle.

DR. HOOFNAGLE: The IgM anti-core test is helpful in diagnosing acute hepatitis B because tests for surface antigen alone can sometimes mislead the clinician basically, and it can go both ways. The surface antigen can be positive and the patient may have chronic rather than acute hepatitis, and this test should separate those two.

It goes the other way, too. The surface antigen may be negative and yet the patient has acute hepatitis B.

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In that situation, what has happened is he has already cleared the surface antigen. Some people clear it very quickly or they get to the doctor late.

So, it is those two situations where the IgM anti-core test is helpful, and as far as what types of studies are necessary, I think those are the two areas where you should focus down. You should look at a panel of patients with acute hepatitis of all sorts and see if this picks up all the cases that are B.

Now, how can you tell they are B? They either have surface antigen or, in followup, they develop anti-HBs, so in these types of studies, it is very helpful to have a serial followup of some degree to show that those people who are surface-negative, but had IgM anti-core, had B, and if you don't have earlier specimens, you can't tell, can you?

So, in these types of things, the serial specimens are needed. The same can be said for IgM antibody to hepatitis A. The other thing you want to know is that this antibody goes away in an appropriate amount of time, and I think with the Abbott test, originally, usually by a year, everybody is negative, because you don't want to pick up a lot of people with IgM anti-core who recovered many, many years ago, and now you think that this is B.

So, I think this is where you need serial

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collected specimens from acute cases. I don't think that this would be a problem as far as laboratory to laboratory reproducibility. I think these are usually EIA tests that are fairly standard, so it doesn't have the problem of the genome test that may operate poorly in the field.

DR. THRUPP: No, but it may have the problem, as Dr. Hollinger indicated, in terms of where a cutoff point is established or how it is clearly established in order to avoid picking up the small amounts that might be present in chronic disease that is not perhaps relevant to your diagnosis of acute hepatitis.

DR. HOOFNAGLE: Absolutely. Virtually everybody with chronic hepatitis B has IgM anti-core, but it's at low titer, so they have to choose a titer that is negative in a panel of patients with conventional chronic hepatitis B.

I don't think you can make it an absolute, though. Even with the current assay out there, with severe exacerbations of hepatitis B, they will come positive on that test, but that is not really a big problem. It just needs to be kept to a minimum.

DR. THRUPP: Dr. Specter.

DR. SPECTER: I would just like to ask for a clarification. I agree completely with your statement about core blood, but in terms of late when you are in the window,

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is M really more valuable, is it of significant level of value compared to total anti-HBc, where you are really late in a response and probably got much more of a G response than an M at that point.

DR. HOOFNAGLE: Well, you see, anti-core will persist for life.

DR. SPECTER: Right.

DR. HOOFNAGLE: So, you don't know that it's acute. It could be someone with acute hepatitis A who had hepatitis B many, many years ago, and risk factors for various forms of hepatitis are shared in common, so people frequently will have antibody to other forms of hepatitis when they come in with an acute.

DR. SPECTER: But you are talking about not a true acute immune response when you are in the window, so is M significant enough to make a big difference then as opposed to total antibody?

DR. HOOFNAGLE: Total antibody won't tell you that it is acute B.

DR. SPECTER: Right. What I am saying is will you find M often enough?

DR. HOOFNAGLE: Oh, yes. The M will last at least three months. It depends again on how you pick the cutoff or how quickly people, what percentage of people are

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positive and how quickly they become negative as the IgM falls off with time.

So, it has to be low enough that people are positive when they are first seen by the physician, when they are first jaundiced and come in, so they should be positive at the start, but not continue positive beyond about six, 12 months.

DR. THRUPP: The window, what are you referring to as the window? One might be referring to window as the period prior to the development of acute clinical symptoms.

DR. SPECTER: No, no, no. The core window is really a time where you have lost antigen and gained antibody to S, and that can be fairly far out. I worry about that time point because it is so variable.

DR. HOOFNAGLE: Eighty percent of people with acute hepatitis B will be surface antigen positive or more.

DR. SPECTER: Right.

DR. HOOFNAGLE: It's just a very small percentage that will clear up early. They will have anti-core, yes, but they will also have IgM anti-core, and that is what says it is acute. The assay corrects both problems with the surface antigen test, and that is why it is valuable. It is not absolutely essential for diagnosis, but it is certainly extremely helpful.

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DR. KADREE: I think it is very important where you are not absolutely sure what type of viral hepatitis someone may have, and how recent it is. I think most times when it is used clinically, that is a case in which we are looking at it.

DR. HOOFNAGLE: One algorithm is you test it for surface antigen, and if they are negative, test them for this. That is one algorithm. The trouble is you have to bring them back a lot. Some people would use this as a first-line test, make a diagnosis, and some people would use it as a second-line test if you haven't made the diagnosis with the first battery of tests, that you throw out someone with acute hepatitis.

DR. SPECTER: I don't understand your comment about having to bring them back. You would have the specimen still to test.

DR. HOOFNAGLE: Oh, that's true. It's putting a lot of pressure on the private physician to understand the ins and outs of the serology. That is what makes it difficult. That is why they frequently depend on these panels, what they call a panel, acute hepatitis panel and a chronic hepatitis panel.

DR. SPECTER: The acute panel now is obviously the total anti-HBc.

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DR. HOOFNAGLE: No.

DR. SPECTER: Well, I am saying it could be, and the question is how much more valuable is M going to be than total, and I understand that it can distinguish acute from chronic, but one wonders how valuable it is under real testing.

DR. THRUPP: I think that Dr. Hoofnagle is saying the data would suggest that the M is valuable, whereas, the G is not.

DR. SPECTER: I guess my question is, is data saying that or is theory saying that?

DR. HOOFNAGLE: The data says that. Otherwise, you have to get them back a couple of months later to see if they have rising titers of antibody to hepatitis B, say, oh, yes, that was hepatitis B.

But one could argue on the other side that it doesn't really matter. If they have cleared the surface antigen, what are you worried about?

DR. THRUPP: Do you feel the data are solid enough to really say in a package insert or in a clinically recommended procedure that if you are looking for a diagnosis, that the lab should always, if the surface antigen is negative, then, automatically, run the IgM as an algorithm?

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DR. HOOFNAGLE: Well, you could say you should run it even if the surface is positive, because they might be a chronic carrier with a superimposed form of liver disease or an exacerbation. So, I think you can argue--there are so many arguments back and forth that sometimes it is better to go with the panel.

The usual panel I believe would be surface antigen, IgM anti-core, IgM antibody to hepatitis A, and antibody to hepatitis C. In hepatitis C, the IgM response isn't very good, so it is not very helpful. It would be nice if it were.

So, that would be the usual panel. Some people would leave this test out of the panel, and just miss a few of the hepatitis B's and misdiagnose it or come back later and do this test. But I think what the FDA needs--I mean the test is established in clinical practice--what you need to know is how to license new tests that come along, and I think it is a pretty simple answer actually.

DR. THRUPP: Do you think that the FDA in order to include this recommendation in the package insert should have quantitative field trials to say just how many patients might be missed by not including the IgM, what proportion? You just said there is a few.

DR. HOOFNAGLE: I suspect that these manufacturers

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could provide that in the testing. If they have a specimen from 100 patients with acute hepatitis when they are presented, and one month later they could tell you how many were missed with the various assays. I am not sure that that would be excessively burdensome to provide such data.

DR. THRUPP: I can predict in the current HMO-driven era that somebody is going to want to know some hard data to say what is the added value of the second test in what proportion of cases to make it cost effective.

DR. HOOFNAGLE: People have that data. I am afraid I don't know it off the top of my head, but those data are out there.

DR. THRUPP: Just as a generic question, is it reasonable for the FDA to ask someone to present or gather that data?

DR. GUTMAN: Yes, we would appreciate if you would reframe the simple answer.

DR. TICEHURST: You said there was a simple answer to performance for IgM anti-core.

DR. HOOFNAGLE: A collection of serially collected specimens from the onset of acute hepatitis.

DR. TICEHURST: That is not real simple. That is simple scientifically, but not simple pragmatically.

DR. HOOFNAGLE: That's true, but it is not as

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difficult as like HCV RNA tests, where there is a lot of things involved.

DR. TICEHURST: Can I respond to the other question that came up about types of recommendations? It depends in part on what the first and second test are and what the company is manufacturing.

As you will recall, we had a question this morning about anti-HCV questions for assays for physicians' office laboratories. We have gotten inquiries about HBsAg antigen tests for physicians' office laboratories. I don't think that particular company is intending to make an IgM anti-core assay.

So, the question becomes but it probably would be reasonable for them in the course--I mean one could say in the course of their studies, as they have the group of patients that they are characterizing their assay in, that they could figure how many people either from single specimens or during the course of serially-collected specimens that they miss with their assay.

If it is another manufacturer who is manufacturing both, I would think the purchaser of that assay would want to know how both those assays performed.

DR. THRUPP: Dr. Gates.

DR. GATES: I also think, looking from the

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manufacturing side, it is important to keep in mind exactly what is involved when you have to set up clinicals that are going in to for a 510(k), and that the idea--no?

DR. TICEHURST: These are all Class III devices.

DR. GATES: Okay, so these would be PMAs, excuse me. But my point is that being in a position of having to review these things to make sure the data is in some sort of form that is understandable and simplified, you have to have fairly focused clinicals, and I think if you start adding too much to them, you are going to start getting pretty cumbersome clinicals, and I don't know, I think to some extent may compromise the data in the sense that you are trying to get too much into one clinical trial.

DR. THRUPP: This does get into the issue of how much will the FDA accept previously published or previous literature data on establishing the validity of a test that was used, and then is the new test identical to or a replicate of a so-called predicate test, in which case maybe they can use old data as opposed to how much do they have to do to produce new data completely from scratch.

I am sure there is going to be judgment calls on this issue, but I am not sure we can settle this.

DR. TICEHURST: Can I respond to that? Freddie, can I respond? We would appreciate your recommendation on

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that. If you remember some of the stuff that Mr. Simms presented this morning, the Commissioner of FDA can ask for alternative types of information, and a lot of times for laboratory assays, that is interpreted as peer-reviewed publications.

The flip side of that, of course, is that we are looking at new assay, and maybe the way to think about that is how much do we know about an assay for a particular analyte over the period of time that that type of assay has been in existence where we could rely on published reports.

On the other hand, how much is known about the variability from one assay to another in published reports that would make that not a good source of information.

DR. THRUPP: At the very least, you would have to establish that the new assay was equivalent to the old with whatever control sense that you would be using.

Dr. Charache.

DR. CHARACHE: I would like to comment on that, but the earlier comment, to amplify Dr. Hoofnagle's simple response, I wonder if we could add to that the requirement that the test be engineered, so it can detect early new disease and ignore the chronic case in which the IgM comes and goes, so you would have your quantitative cutoff.

DR. HOLLINGER: I think that is important. I

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would imagine that if you go back, maybe there is some data on this, but it may well be that although we do now test the IgM anti-HBc at, say, 1 to 1,000--I am just going to use the number here because there are different dilutions--but let's say at 1 to 1,000 or 1 to 1,071, that if that were raised to 1 to 2,000, maybe we would eliminate, not eliminate any of the acute cases, but would eliminate most or more, a larger percentage of the chronic cases that occur during reactivation of their disease or exacerbation of their disease without losing any of the acute patients, because they do have fairly substantial antibody levels during acute disease.

You know, it is sort of an arbitrary thing that was set I am sure initially with not quite realizing, any of us realizing about the IgM potential in patients with chronic disease. It wasn't really considered I think initially, so that sort of wiped out this black and white distinction that we had and sort of made it more of a gray problem.

DR. THRUPP: I think we have come to a reasonable consensus at least on these discussions. Let's go to 1b, what types of studies are necessary for establishing the performance of assays for the HBV DNA?

DR. HOOFNAGLE: Again, the question is what do you

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use this test for, and this is a very difficult issue because most patients with chronic hepatitis B have high levels of HBV DNA that can be detected by direct methods with amplification, as John said.

These are astronomical levels. People in HIV don't realize how hepatitis B, there can be 1,000- or 10,000-fold higher than your HIV level or HCV level.

The difficulty is that there is actually a very broad range of how much HBV DNA can be detected in serum, and patients who have the so-called healthy carrier state, who are surface antigen positive, but have minimal liver disease, they also have HBV DNA in their serum, but it is at a low level and it is usually not detected by these direct hybridization assays.

So, the direct hybridization assays have been very useful clinically because if the person was positive, they had chronic hepatitis B, and if they were treated and responded, they would become negative. It was a criteria that we used for a response to antiviral therapy.

But when more sensitive tests came along for HBV DNA, we found that everybody was actually still positive at the end of therapy and in followup at low levels, but it wasn't very clinically meaningful and that their liver disease had gotten better.

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This even goes on to the following point that if you clear hepatitis B, and develop no more surface antigen to make antibody, sometimes small amounts of HBV DNA can still be detected, usually not in the serum, but in the liver it is still there.

So, this is a much more difficult disease than hepatitis C in talking about this assay, because if you have a very sensitive assay, it is not very clinically useful because low levels don't seem to be injurious.

So, the real question is what is the assay for. Now, the other problem that has come along in the last year or so is that with antiviral therapies, with nucleoside analogs, you can make HBV DNA negative in everyone, but it is still there if you use PCR.

So, the standards for these assays are difficult, and for HBV DNA, I would say that a qualitative test is absolutely essential, a quantitative test is almost meaningless.

Here is where you need to know the titer of virus, and when you get down to low titers, we still don't know their clinical significance. If you have 100 virions per mL of HBV DNA, that is probably insignificant, no liver disease, probably good prognosis, but maybe not, we don't really know. If you have greater than a million, you

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usually have disease, you usually have chronic hepatitis.

So, I would say here you have got real problems in establishing performance of the assays, and really have to focus on their purpose, and I believe they have to be quantitative.

DR. THRUPP: That is quantitative with a cutoff.

DR. HOOFNAGLE: Well, they will have to be. If they are direct hybridizations, you can't go too much below  $10^5$  to  $10^6$ . That is about as good as you can go.

DR. THRUPP: In a way, that almost becomes a qualitative if it is going to be negative.

DR. HOOFNAGLE: I am sorry, I mean qualitative, yes. I hate those two words, because they are just a letter apart. They have to be qualitative, they have to give an amount of HBV DNA.

DR. TUAZON: Quantitative.

DR. HOOFNAGLE: Quantitative. It's after lunch. Quantitative, you have to have a titer of HBV DNA, plus or minus is not good enough.

DR. THRUPP: Except that if you did the direct hybridization assay, which is only detecting higher levels, a positive qualitative in that assay would give you, in essence, the answer you want clinically.

DR. HOOFNAGLE: Greater than a million, say.

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DR. THRUPP: So, it could be a qualitative assay.

DR. HOOFNAGLE: Yes.

DR. THRUPP: That gives you a relevant clinical response.

DR. KADREE: Dr. Thrupp, if you have certainly a qualitative assay using direct hybridization would be adequate clinically in terms of identifying chronic disease, however, since as was pointed out, we don't fully understand the direct relationship between the titer and the degree of actual disease or potential disease, I think if we are talking about bringing new tests on the market, we should try to establish what that is, so then it becomes important to look at it quantitatively rather than just qualitatively.

You know, once we have determined, for example, if you have less than 100,000 particles, it is insignificant, for example, then perhaps we needn't worry about it so much, but I think until such time as we have an understanding that for tests that are coming on the market, it would be better to look at it quantitatively.

DR. THRUPP: I am not sure. I think that the FDA has to look at the intended use in a package insert, and the intended use at this point in time has to be based on available clinically relevant data, and if I heard Dr. Hoofnagle say that there aren't, at this point in time, that

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all cases that have very low levels of DNA present in chronic carrier states are still going to have the same risk for ultimate hepatocellular carcinoma, then, we might say that we do know that there is clinical significance.

DR. KADREE: But that is not true.

DR. THRUPP: He is not saying that, and therefore, I am not sure whether, at this point in time, that we would want to have a package insert at least require the quantitative assay.

DR. HOOFNAGLE: I think I will make one point, again, HBV DNA is not a good test for diagnosis. I would say it is a bad test for diagnosis. It doesn't separate acute from chronic, it has got some problems with false positives, it is expensive. So, we are talking about a test for monitoring.

In the context of monitoring, we are talking largely about therapy, not about assessing prognosis in someone that you have just met, therapy. The endpoint of therapy, the first endpoint that you reach is clearance of HBV DNA. That happens first, and then with any luck, they clear the e antigen, and then their enzymes become normal, and then if they are real lucky, they become surface antigen-negative. But HBV DNA is the first thing to happen.

So, it is helpful during therapy to test it and to

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show that it goes below your level of detection by hybridization assays. As such, it is very nice to have a titer, so that you see if it is going down, if it is going in the right direction, as well.

But you are right in a way, that all you would need would be a qualitative test, right? You know, the trouble is all qualitative tests ultimately are quantitative. You are above 100,000 or you are above something.

DR. HOLLINGER: You also have a less expensive qualitative test, actually, in the e antigen. Most e-antigen positive patients have very high concentrations of virus. I mean, as Jay said, maybe as you are going down in treatment, that is a little different story, at least initially, but almost all the e-antigen patients are going to have real high concentrations.

It is in the anti-e group where you have a little more difficulty because there are variants, pre-core variants, and others in which you may have antibody to the e present, that have very high concentrations of virus. Those patients in HBV DNA can be useful in terms of determining therapy and things of that nature. So, that may be where you would want a quantitative assay to be used at that point.

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DR. KADREE: What about patients who are immunocompromised and who may not mount--

DR. HOOFNAGLE: They usually have high levels, not difficult to miss.

DR. HOLLINGER: And are usually e-antigen positive unless they have the pre-core.

DR. HOOFNAGLE: So, you use those tests to assess whether a person should be treated and the success of the treatment is what I would think the major use of this test would be.

DR. THRUPP: Dr Charache, and then we should go on to No. 2.

DR. CHARACHE: I just wanted for the sake of completeness to get back to my earlier question. This is for the full range of capacities, and I am sure we are all looking forward to the microchip in which all the causes of hepatitis are on the same chip, whether they are viral or genetic or whatever they are.

So, I can see a test format in which it could be a simple diagnostic and a discriminating diagnostic for the cause of hepatitis. We haven't heard any of those now, but I don't want to prejudge that they won't happen.

DR. THRUPP: Let's go to No. 2. Are there recognized indications for using a quantitative assay for

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anti-HBs, and if so, what types of studies are necessary to establish performance?

DR. HOLLINGER: I will tackle that with the vaccine. Basically, that is where a quantitative anti-HBs might be useful, but it has some relatively limited usefulness. There does seem to be a level, somewhere around 10 to 20 million IU/L at which protection seems to be apparent.

Some of the very early studies suggested and showed that if a person who was immunized didn't reach that level or higher, they were susceptible to acquiring under certain circumstances hepatitis B if they were not protected.

That is not true once they reach that level and come back down to the lower level. That is, if they went up to 100 or 200 and over several years have now gone down below 10, they are probably still protected in the vast majority of cases.

So, it is only important of where they reach that level to start with, and therefore, after vaccination, it doesn't matter where you do it, but something like 4 to 12 weeks or so after the final dose of hepatitis B surface antigen is given at six months, if those patients are tested and found to have not achieved this level, then, it is

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important to let them know that, particularly if they are in a high-risk group, that they may not be protected against hepatitis B.

So, in that case, quantitative assays for anti-HBs are useful, and we certainly recommend it. We don't know also, there is a suggestion that protection is present even though your antibodies may become non-detectable or go below 10 after many years. The fact is we don't know over a long period of time whether that protection will still be there.

Most of these studies that this information comes from or with the plasma-derived vaccine, which is no longer available, we don't know with the recombinant vaccine if that is going to be the case, but the key thing is that the presence of that antibody may be useful in determining whether somebody needs a booster later on or we just make a decision.

I personally don't think it is that critical. I think that one could make a decision that at a certain point, one booster dose five years, 10 years or something, is going to be sufficient. You wouldn't need to do a quantitative assay for that.

At least initially, in my opinion, it is important to know that they have at least attained a reasonable level of antibody in order to reassure them that they probably

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have protection against hepatitis B.

DR. DeFOREST: And you would do that after the third dose?

DR. HOLLINGER: Yes, after the third dose. I mean the only other time it would be useful is if you had a couple and they wanted to know when they could resume relationships, and after the first dose or second dose you could also test their blood, and, of course, if it was above a certain level, then, the probability of their being protected would be fine, and you could then reassure them that they didn't have any further risk of acquiring hepatitis B.

DR. THRUPP: There is a practical issue here of the real practical world as opposed to the real world, and you have expressed the data supporting post-vaccination testing ideally for everybody that gets the vaccine.

DR. HOLLINGER: No, not for everybody. I don't think that is really necessary.

DR. THRUPP: At least for high-risk groups.

DR. HOLLINGER: For high-risk groups, I think that is important that they know that, not for the infant that is being immunized, and so on, I don't think that is necessarily so important.

DR. THRUPP: There are I don't know how many

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millions of health care workers that would be in high enough risk to be considered high-risk groups, and ideally, they ought to be tested, you are saying, to make sure that they get to a certain level. You didn't say what that level would be. It can't be just 10 because it has got to be up there somewhere, and we could argue, or you could produce data on that.

DR. HOLLINGER: The data would suggest that if it is above 10 to 20, there is some risk in between 10 and 40, but you are right.

DR. THRUPP: But in the real world, many, I don't have data on what proportion, of hospital-based health care worker programs have not been calling for post-vaccination testing. So, we are talking about an order of magnitude of increment--costs are not our main issue I know--but it is a new algorithm for many institutions if you require post-vaccination testing.

Should we encourage the FDA, in looking at this, to include an algorithm that makes that strong recommendation, in which case it has a lot of implications out in the real world?

DR. TICEHURST: May I bring up a point, please?

DR. THRUPP: Yes.

DR. TICEHURST: Before I do this, I want to ask my

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colleagues from CDC that are here if the--I was going to read a quote from the MMWR recommendations and reports on hepatitis B vaccine, which was issued in 1991--are those still in effect? Yes? Okay.

This is under the subject of Post-Vaccination Testing for Serologic Response.

"Such testing is not necessary after routine vaccination of infants, children, or adolescents. Testing for immunity is advised only for persons whose subsequent clinical management depends on knowledge of their immune status, for example, infants born to HBsAg-positive mothers, dialysis patients and staff, and persons with HIV infection. Post-vaccination testing should also be considered for persons at occupational risk who may have exposures from injuries with sharp instruments because knowledge of their antibody response will aid in determining appropriate post-exposure prophylaxis. When necessary, post-vaccination testing should be performed more than six months after completion of the vaccine series. Testing after immunoprophylaxis of infants born to HBsAg-positive mothers should be performed from three to nine months after completion of the vaccine series."

There is another point I would like to read here with regard to vaccine efficacy and booster doses. Since I

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don't have it highlighted, I can't find the exact thing, but I do recall a very distinct recommendation--that there was no data to suggest that booster vaccination was necessary at the time this was written.

DR. HOLLINGER: For 7 to 10 years.

DR. TICEHURST: Right, and the point for bringing that up in part is because CDC is a sister agency of FDA and the Department of Health and Services, and we very often use their guidelines as points of reference, if not guidelines to be strictly followed.

DR. THRUPP: The wording in the CDC guidelines is often not in strong--I mean many recommendations are softly worded to allow for flexibility, and I think I heard you say could be considered, which is not exactly a very strong recommendation, and I think many institutions have elected to do the testing of the high-risk person at the time of an injury rather than instituting routine post-vaccination testing. So, I would suspect if you published a proposed guideline for a package insert, whatever that said that you should test it or it is strongly recommended, you would have a lot of objections from the employee health service-based individuals.

DR. HOLLINGER: But if you did it at the time of injury, you are back to square zero, because you don't know

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what they ever achieved at the first place, whereas, if you know that they achieved adequate response to their vaccination, then, at the time of injury you could at the most just say we will give you a booster injection of vaccine.

On the other hand, if you wait until that period of time five years, 10 years later, and they get a needlestick exposure, you now don't know if you are dealing with somebody who was ever protected in the first place, therefore, are obligated, in my opinion, to give them HB in addition to a vaccine at that time, as well as you might want to test them.

DR. THRUPP: That is reasonable if they have no antibody at this 10-unit, whatever, cutoff, yes, the latter is what you do, but if they have antibody, and it has been five years, whatever, if they still have a 10-unit antibody, then, they are probably okay.

DR. HOLLINGER: I would not want to wait two days. The time to treat and to try to do that from a prevention standpoint is yesterday in terms of giving protection against infection. What you are really saying is by the time you wait and they call you, and you do the test, and you get the results back, you have waited now about two or three days.

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DR. THRUPP: Dr. Hoofnagle.

DR. HOOFNAGLE: I am not sure a quantitative assay for anti-HBs is very needed clinically. These have been very important in vaccine studies and in studies of liver transplantation, but clinically, as Blaine has said, the main thing is this 10-milliunit cutoff, and I think in many of the assays, they have a gray zone, so that if you are positive in the gray zone, you have to say the immunity may not be complete. So, I think it would be helpful to have assays for anti-HBs include a gray zone that would be in this less than 10-milliunit range, and these people, the question always remains if they are immune.

It also occurs in people who have never been vaccinated. You see these low levels of anti-HBs, they are usually false positives. That is the other reason for using a gray zone. So, I would recommend that the CDC, in evaluating new tests, look for this gray zone and include it in the evaluation and in the description of the test. I don't think that is hard, and that is only semi-quantitative, that is not giving you titers.

DR. THRUPP: Just for the transcriptionist, you meant FDA, I think in that comment rather than CDC.

DR. HOOFNAGLE: Yes.

DR. TICEHURST: May I ask a question for

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clarification? It goes back to one of the sort of pre-queries I introduced. It would seem to me from what I am hearing that the purpose of the gray zone would be in the range more of around 10 million IU/L up to 20 or 30, but not below 10. It goes back to the question I posed, not up here, is there any utility for detecting between zero and 10.

What I heard Dr. Hollinger saying is the people he is worried about are those who have been recently vaccinated, who have a response in the less than 30, 40 range. If they are less than 10, I think those are the people that you would--what I hear you saying is those are the people who have not had any kind of protective response.

DR. HOOFNAGLE: Oh, no, they would boost quite well if you gave them another shot of vaccine, for instance, whereas, if they were truly negative, they may still remain negative with further boosting. I think it is helpful to have a low positive gray zone.

DR. TICEHURST: So, you would want that gray zone to cover what range?

DR. HOOFNAGLE: Whatever they can measure down to.

DR. HOLLINGER: You need to know what is reactive, what is truly reactive and what is negative or non-reactive, so--for other reasons, not just the vaccine. If you are

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talking about vaccine, yes, I do think it is important to know where on their scale of things, this 10 to 20 IU/L would fit, and therefore, if it was above that, one could have a more secure feeling that the vaccination was probably at least, as much as you can tell, successful.

But for other things, just immunity to a past infection, then, any reactive level I think is important in that in association with the total anti-HBc for those individuals.

DR. THRUPP: Dr. Tuazon.

DR. TUAZON: What percent of people are we talking about who don't mount a protective antibody response with three injections?

DR. HOLLINGER: That really varies. I was reading an article the other day from some studies down in Central America, in which like 40 percent were negative out of a group of people that were young adults that were immunized for reasons that aren't clear to them, but I have a feeling that these levels can range anywhere--I mean in the field trials, in the vaccine studies, probably 90, 95 percent often would have good detectable antibody levels, but when you get into routine situations, those numbers have not been holding up, I don't believe, to that level.

DR. TUAZON: If you give them another shot, would

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they boost?

DR. HOLLINGER: Yes.

DR. THRUPP: For those of we health care workers who happen to be in the "elderly" age groups, which is one of the groups that don't respond, would you go so far as to say that that subgroup should have routine post-vaccine testing?

DR. HOOFNAGLE: No, you should practice safe sex.

[Laughter.]

DR. THRUPP: With that, let's go on to No. 3.

In clinical studies, for establishing performance of HBV-specific assays for monitoring chronic hepatitis B, what monitoring indications should be considered, and what endpoints are used in the clinical studies?

Some of this has already been alluded to, but perhaps we can summarize it.

DR. HOLLINGER: Maybe, John, you could tell us what you mean by "monitoring"? Is this just like following patients along for a period of time to see what is happening to them? I mean most of us would just monitor patients as time goes on in a couple of ways.

If they were e-antigen positive, certainly we would look at their enzymes, to look at their reactivating or if their enzymes are stained normal or what.

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Secondly, we would look at their e-antigen anti-e status if they were e-antigen positive. As you know, perhaps up to perhaps 15 percent a year might seroconvert for e-antigen to anti-e 5, 15, percent.

If they were surface antigen positive, we might look at that, although the data would suggest that probably they become surface antigen negative probably less than 1 percent a year over a long period of time, so it is not very likely that they will become HBsAG negative.

In terms of HBV DNA, we would rarely monitor for a long period of time like getting HBV DNAs unless we are talking about treating patients and something of that nature, but the monitoring would be fairly limited and would be mostly looking at their liver disease in monitoring, not so much their serologic markers.

DR. TICEHURST: I think you answered your own question. Thank you.

DR. HOOFNAGLE: But again monitoring for therapy, you would want to do e antigens and HBV DNA in preparation of treatment, and then at intervals on and after treatment, you would probably repeat that depending on the antiviral, so those tests are very valuable in looking at therapies of hepatitis B that are coming along, it is getting to the point where therapy for hepatitis B will be almost every

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patient.

I do think these tests need to be approved by the FDA and standardized for HBV DNA. There is an e test out, you know, a test for e, but for HBV DNA, it is very important.

Let me say something about the test for HBV DNA. Unfortunately, the very low levels become important when someone is on antiviral therapy, and the performance at low levels of HBV DNA by hybridization assays has not been good, in our hands at least, and that is one of the critical things the FDA should look at in approving these drugs.

The cutoff levels, when you get around there, they don't perform very well.

DR. TICEHURST: May I make a comment and ask a question? The comment is--and I have alluded to this in some of the other questions--the cutoff for an assay for a particular analyte can be different for different indications for use. You have made the point previously why one would want to have a higher cutoff for some indications for a HBV DNA assay, a lower cutoff in the case of monitoring therapy, but we are getting an answer to the question.

The question--I have forgotten the question--I will try to think of the question.

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DR. HOOFNAGLE: Well, there may be other tests coming along for monitoring like quantitative e levels may be good, and it really will depend on the antiviral. So, I think these types of tests will be coming in to you in relationship to antiviral therapy, what happens with therapy, and how these tests help in predicting outcome or monitoring outcome or determining cure.

DR. TICEHURST: That was my question. I think it is reasonably well established at this point that the concentration of HCV RNA can be used to some extent to predict prognosis of response to therapy.

Is there a similar knowledge for HBV?

DR. HOOFNAGLE: It is not very predictive, but again we are usually dealing in high levels. When you deal with the very low levels, people around 1,000 or 10,000, that does seem to be associated with mild disease and a fairly good outcome, but whether you are 1 million versus 10 million versus 100 million HBV DNA, there doesn't seem to be too much difference clinically overall.

DR. HOLLINGER: Although there is a lot of academic things we are interested in perhaps when we talk to the patients, and so on, from the practical standpoint, it probably doesn't mean much.

For example, if you had a woman who is pregnant,

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there is a correlation between the DNA concentration of HBV in their blood and the probabilities of transmission to the infant, a very good correlation with that. Now, if they are e-antigen positive, that is the correlation, but if they are anti-e positive, having that piece of information would say you have a higher probability, so what are you going to do differently.

You are going to give them hepatitis B immune globulin and vaccine when the child is born anyway, and then take your chances that most likely you will prevent that infection, so it becomes an academic, it is the reason we ask people that refer their patients to us basically, but I think from a practical standpoint, it doesn't have much benefit.

DR. THRUPP: Let's go to Question 4.

Are there other combinations of assay and indication for which the panel would like to make recommendations? For example, we have just heard Dr. Hollinger and Dr. Hoofnagle suggest that hepatitis E under some circumstances is going to be relevant.

Any other comments? Dr. Charache.

DR. CHARACHE: I think it is the last question, so I will bring up the issue that came up a little bit earlier, which has to do with predicate tests and assessment of

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predicate tests or devices.

I have been thinking about that and there were a couple of issues that I would wonder if we should be addressing as you think about using a predicate test as a monitor of a new test development.

I think we are all concerned about the comparability of any predicate test that is used and whether it was designed for the same purpose as that which you want to address with your new test.

I think what we have been talking about is beautiful illustration because many of the predicate tests wanted to detect any marker for hepatitis B, whereas, here, we are addressing specific diagnostic and therapeutic uses of it.

So, you might need to know more about the clinical status of the patients that were used for a predicate device and its comparability for the purposes for which you want to use it as opposed to just saying these two tests can both measure IgM for HB core.

I think this also applies to the issue of whether you can use stored sera. A lot of things happen to stored sera, and again I think it would be a matter of comparability, but I was thinking particularly as we talked about again the IgM assays, of ensuring that these samples

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hadn't been frozen and thawed and what have you, and they still were a good predicate for subsequent testing.

These are very precious samples, so you would want to get maximum use of them if they are still good, but I think these are the tip of the iceberg of the kind of questions you would want to have thought about.

DR. HOLLINGER: Are you talking here, John, also about anti-core in general?

DR. TICEHURST: Because of the limitations in time, again, we picked a few key examples. That last question appears after C, it also appeared after A. If you look at the tables that we put together in the first part of the information you were sent, there is a huge list of permutations of different analytes for different indications.

We haven't talked at all about the indication of diagnosis of acute hepatitis B other than in reference to the IgM anti-core assay. We haven't talked at all about diagnosis of chronic hepatitis B. We haven't talked at all about HBsAg testing during pregnancy.

Susceptibility prior to vaccination, evidence of past infection. These are all different indications for hepatitis B markers, and we have seven different markers to consider here. There is a lot of different permutations

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there, and because of limitations of time, we had to pick some things that we thought were key. There may be some other ones that people on the panel are particularly concerned about, or if you want, I can spend a minute and find some that I was a little less concerned about, but didn't feel we had time to talk about.

DR. HOLLINGER: When you are looking at these tests with hepatitis B or anything else, there are some concordant results or discordant results that are really critical.

First of all, we need better anti-core tests. The false positive rate is too high. There are some very good probabilities of looking at this, and I think, like dithiothreitol, and other things, which might bring this false positive rate down, and that needs to be assessed.

I think it is important. Personally, I think it is important to do an anti-core test with the HBs antigen test, because it gives me strength of validity. Now, you say the neutralization test, I never have done a neutralization test in my life, but I always do an anti-core test, because if I find an HBs antigen that is positive and an anti-core that is negative, then, that is very suspicious to me that that is a false positive HBs antigen.

They are usually of low concentration, they are

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often in patients who have a heparin lock in place or they have got a coagulopathy or they are receiving heparin because they are in an orthopedic ward, and things like this. Those are the classical ones in which the HBs antigen is positive, anti-core is negative, a little thrombin clot in there, and it goes away after a day or two if you let it sit in the refrigerator.

So, the anti-core, HBs antigen group is important. The other one is the antigen. You don't see e antigen in the absence of HBs antigen. I think maybe I have seen it maybe once in 25 years, I am not sure if that was really true or not, but in essence, if a person is e-antigen positive, he had better be HBsAg positive.

It is unusual to find anti-HBe and HBe antigen, those two positive at the same time. You can find them, but it is an unusual finding. So, there is a lot of little things in here. The same with IgM. The IgM antibodies are always--the total antibody is always positive in those instances. It is rare to find an IgM--I have not seen an IgM that is positive in which the total is negative. Obviously, the reverse happens frequently.

So, I think those kind of things are items that are just as important in validating many of the tests that we do, and give us a sense of security that we ordinarily

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would not have in a laboratory.

DR. THRUPP: Those are pertinent points. Are you implying to our FDA colleagues that you feel that the paired tests, the algorithms should routinely include the second test?

DR. HOLLINGER: I would like to hear some discussion on it. I am not sure that--I don't know, in other words, if that is a clinical question more, I mean that a physician ought to order those tests or not, but I mean I would not order just an HBs antigen test on a patient unless I know the patient, if he has got chronic disease and I want to know if his HBs antigen has changed, that is all I will order. If it is a new patient coming in, and I am looking at that, I would want to have that except that now they are doing--they do neutralization tests, and that is okay also.

DR. THRUPP: The points you were making would be amenable to evidence-based decisionmaking in terms of what goes into an FDA package insert, so presumably there could be enough data produced, so that it could be laid out how often, whether it's 1 percent or 2 percent, or how often the SAT would be a false positive, which could be corrected by adding a second one, or so you could at least get a quantitative idea of how often this would be relevant, so

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perhaps that kind of data would be within the purview of what the FDA might like to look at.

DR. HOLLINGER: The problem is in doing something like this, you don't know why the clinician ordered it. As I said, if it were in there that you should do the HBs antigen with the anti-core, if I am understanding you--

DR. THRUPP: In terms of what the FDA has to look at for approval of a new test, we are not dealing with what the physician ordered, we are dealing with prospective studies that are going to validate whatever is being looked at. The package insert eventually will deal with what the docs are going to order, and that is a whole bag of worms, too.

Any other comments? Dr. Ticehurst.

DR. TICEHURST: I think Dr. Hollinger in his last comments alluded to a number of things that I might reflect on that maybe could open some other discussion.

I think one of the things he said is that at least in your practice, that the concept of two-step testing for HBsAg is not a hard and fast one for diagnosis and monitoring, just like we talked about for anti-HCV.

You raised questions about the specificity of the total anti-core assay as they current exist and measures that are being taken to try to improve their specificity.

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My understanding is this has been a huge problem for testing of blood donors and donors of blood products.

The question would become there, for the clinical indications for the total anti-core assay, how do we determine its specificity and if you change the nature of the analyte with DDT, for example, so that you remove IgM anti-core, does that change its performance in terms of one of your indications, which was acute hepatitis B.

Couple the indications that we have considered for the total anti-core assay in addition to what you have mentioned, would be in evidence of past infection, susceptibility testing prior to vaccination, and it could also be used as an exclusionary test, for example, for doing post-vaccination response.

I just wonder if anybody wanted to comment any further.

DR. HOLLINGER: I agree with you. I think the anti-core test is an excellent test to use for pre-vaccination--if you are going to look at somebody where they need to be vaccinated, that would be the test I would choose.

DR. TICEHURST: But how do we demonstrate its specificity particularly when it is the only positive marker?

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DR. HOLLINGER: That would be true for I think the whole anti-core system, I mean not just that alone, but also with patients who are HBsAg positive. It is an important issue. I mean you would really like to have a test that would have much less false positives with it and be more truly positive.

Again, in my experience, when you find that, it is of a low level. It is usually the low level are the ones that are the problems, not the higher levels.

DR. TICEHURST: Try to consider what the implications of a false result are in each setting. If you consider the implications of a false positive HBsAg result for the indication of pre-vaccination susceptibility testing, that person doesn't get vaccinated, and presumably they are being tested because they are at high risk.

If you consider the implications of a false negative in that situation, the person gets vaccinated, which is probably not a concern.

DR. HOLLINGER: From what you are saying, that is probably from a practical standpoint. See, I would not do that, I mean personally. I mean I would do the anti-core. If it is positive, I am not going to recommend no vaccination. Now, I follow that up with a HBsAg and an anti-HBs.

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It means either the person is previously infected, and they will be anti-HBs and anti-HBc positive, or they are currently infected with an HBs antigen that is positive, so I clearly want to follow up and see what that is before I would definitely, particularly on a high-risk person, before I would say you don't have to worry about it. I would just go with--

DR. TICEHURST: It wouldn't stand by itself.

DR. HOLLINGER: No.

DR. THRUPP: Any other comments?

We do need a break. Freddie reminded me. We will take 10 minutes. Thank you.

[Recess.]

DR. THRUPP: Please reconvene. Let me just remind those in the audience that at the end of the formal discussions, we do have an opportunity for industry response or other audience participants, such as CDC, et cetera, to offer any additional comments before we close.

Secondly, I would like to have the panel consider one point, which Dr. Charache had brought up, that we didn't really pursue with more definitive recommendations concerning B, namely, that the generic example is hepatitis B total core antibody, which we have heard several comments there is data that it is not performing very well, yet, it

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is out there as a so-called predicate test, and we might for later discussion come back to what should the FDA be encouraged to do to encourage the industry and medical science to do to clean up a predicate test that is out there that does have problems.

For now, let's go on to Dr. Ticehurst, who will summarize hepatitis A for us.

### **FDA Presentation**

#### **Hepatitis A**

DR. TICEHURST: We are going to A, and this general issue is one that in the material that we sent to the panel was presented last, but actually I presented first and then last because I wanted you to think about it.

[Slide.]

We are going to focus on assays for total anti-HAV. If you like, later we can discuss assays for IgM anti-HAV or even potentially assays for HAV RNA, but I think we learned a lot from the discussions for IgM anti-core and the discussions for anti-HCV that we can extrapolate with regard to IgM anti-HCV.

So, focusing on total anti-core, as we have said over and over again, the cutoff could vary with the indication, and I neglected to put this statement in the material that was sent to the panel, but one thing that

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everybody should understand is that the concentrations of anti-HAV that developed after a natural infection are generally much higher than those that develop after vaccination or passive immunization.

If you look on page 747 and figure 15 in the chapter on HAV from Field's Virology, Third Edition, you can see that very graphically. This is the figure that Stan Lemon put together a number of years ago. For those in the audience who can see this easily, the black bar on the far right is that developed after natural infection, the black bar next to it is that from inactivated vaccine, which are the currently licensed vaccines.

It is generally about a log different, if not two logs different for natural infection versus vaccine. So, what cutoffs are appropriate?

[Slide.]

Again, I flipped the order of discussion compared with what was in the material that was sent to you. The first indication would be testing for total anti-HAV as evidence of immunity including pre-vaccination susceptibility. Now, that is a recognized indication at this point.

We are getting inquiries now about highly sensitive assays, and the question that comes up is are

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there recognized indications for such highly sensitive assays. The recommendations for hepatitis A vaccines that were issued by the Advisory Committee on Immunization Practices in December of 1996, through another MMWR recommendations and reports, at this time are for no post-vaccination testing.

However, it is possible that highly sensitive standardized assays might be indicated for: certain populations if they had a significant frequency of not responding to HAV vaccine, for example, perhaps dialysis patients; certain individuals, if knowledge that we don't yet have about the duration of protective antibody levels led to recommendations for booster vaccination.

Such standardized assays could also be very useful for assessing the immunogenicity of a candidate vaccine. That would be vaccines that aren't currently licensed, and that is really not within the purview of CDRH. We are concerned with clinical diagnosis and monitoring, but such an assay would be useful in that realm, too.

[Slide.]

If you are going to have a high sensitive assay, what types of studies would be appropriate for determining clinical sensitivity and specificity. Here is an example of such a study. Keep in mind again what I said before, that

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the levels of antibody after a natural infection are much higher than what you get after immunization with inactivated vaccine.

The assays that are currently marketed tend to have cutoffs that don't pick up the early responses to vaccine. Even though these antibody responses are detectable when one develops a home brew, highly sensitive assay, they are not usually detectable until after the second dose of vaccine or sometime after the first dose of vaccine.

Here is an example of such a study to validate a cutoff. You could have one group of people who are likely to have very low, but protective concentrations of anti-HAV, and these could include people who have received immune globulin or people who are within a few weeks of having received their first dose of HAV vaccine.

These would presumably be used to verify the cutoff on the right side, those people that ought to be positive, and for verifying the cutoff on the left side would be people who are unlikely to have been exposed to HAV.

On the other hand, one could say, well, it's just as sufficient to determine the analytical sensitivity and specificity for such an assay.

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[Slide.]

If you are going to do this highly sensitive testing, one should consider what standards for immunity to hepatitis A virus exist. These would be valuable, if not essential, for evaluating claims or implied claims of detecting evidence of immunity.

Now, what do I mean by an implied claim? It has been our impression thus far--and maybe the panel should correct us--that if a manufacturer wants to make a highly sensitive assay for anti-HAV, that the implied claim is to do post-vaccination testing. Of course, you can get evidence of immunity whether you acquire it from vaccine immune globulin or from natural infection.

The types of standards I am referring to would be laboratory standards, and such standards could include a quantified reference reagent, a practical reference assay, or both of these used in combination.

[Slide.]

Two such standards might be--actually, these are the only such standards I am aware of at this point, there might be others, and we would appreciate advice on that--one would be the World Health Organization's so-called anti-HAV First Reference Preparation.

In the course of developing data to support

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licensure of the two currently licensed hepatitis A vaccines, the manufacturers developed home brew assays that detected 10 to 20 IU/L--referring back to this preparation--as evidence of immune response. That cutoff in essence did not correlate perfectly with the development of neutralizing antibodies, which are usually accepted as the standard of immunity.

It should be pointed out that this preparation, even though it's quantifiable, was developed from post-infection sera for the purpose of assessing anti-HAV and immune globulin. If I remember correctly, the preparation was actually generated at the Center for Biologics Evaluation and Research a number of years ago.

Of interest is a recent study by Stan Lemon and his colleagues where, by using a number of different assays, determined that the kinds of antibody that were generated in response to vaccine are qualitatively different from the antibodies that are present post-administration of immune globulin, so maybe this isn't the best reference preparation for looking for a vaccine response.

Another type of standard would be assays for neutralizing antibodies to anti-HAV. These are recognized to correlate with protection, as I mentioned a minute ago, but they are really very cumbersome.

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There are a few cytopathic strains of hepatitis A virus, but mostly they are not, and these are very difficult assays to do, and not the kind of assays that manufacturers are keen on having or finding participating laboratories to work on for the purpose of evaluating a claim for a highly sensitive assay.

[Slide.]

So, the questions become--and these are questions that we pondered rather than the formal questions for you all--are there appropriate standards for assessing evidence of protection during studies to establish the performance of new, particularly highly sensitive, assays for total anti-HAV? And is there a minimum concentration of anti-HAV that has been accepted or could be used as a criterion for immunity? That would be analogous to the 10 IU/L that has been established for HBV.

[Slide.]

Now, moving to a different indication, which is somewhat similar to the previous one, that would be diagnosis of past infection.

What would be the appropriate criteria to recommend for studies to determine the performance of new assays and presumably again, this would be a total anti-HAV assay. This one, because it is past infection, wouldn't

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need to be as sensitive as the ones we were talking about before.

Here are some examples of the kinds of criteria that could be included. Clinical sensitivity, inclusion criteria, could be historical or prospective evidence for acute hepatitis A at least one year before collecting specimens for studies.

The reason for greater than a year is because these are assays for total anti-HAV, and we want to be sure that they are detecting IgG anti-HAV, and not IgM, and the criteria could include in that period at least a year prior, having positive results for an IgM anti-HAV assay, signs and symptoms of acute hepatitis and biochemical evidence of hepatitis. It would be optional, of course, to detect HAV in any specimens collected during the prodrome or the acute phase.

Specimens would be included if they were shown to contain IgM anti-HAV. These would be the specimens that are going to be tested for the new assay.

[Slide.]

Now, if one was characterizing this with another example of constant criteria that could be looked at for the performance of such an assay, it would be to use a comparison between a new assay and an older comparative

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assay to look at prevalence, and in so doing, one could also estimate the clinical sensitivity and specificity by comparing the two assays.

But just as we were talking a few minutes ago about total anti-core assays, it is very difficult to determine the specificity of an isolated total anti-HAV result when you can't detect it with another assay.

Also, we come back to the issue that we posed before, the cutoff could vary with the indication, and you can see how this can get a lot more complicated if the comparative assay is a highly sensitive assay, and the new one is not so sensitive and vice versa.

[Slide.]

Here are the questions for the panel.

What indications are recognized for highly sensitive detection of total anti-HAV?

What types of clinical studies area appropriate for establishing the performance of total anti-HAV assays; one, that are highly sensitive if such uses are indicated; or when indicated for diagnosis of past infection with HAV?

Again, are there any other combinations of assay and indication for which you folks would like to make recommendations?

### **Open Committee Discussion**

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DR. THRUPP: Are there any other questions of Dr. Ticehurst before we respond to his questions? Dr. Hoofnagle.

DR. HOOFNAGLE: It seems like that the anti-HAV tests that reliance on comparison to previous assays would be of great value in evaluating new tests, because as you say, when you have a natural infection with HAV, you make high levels of antibody. It is not like in hepatitis B where you might have low levels of anti-HBs. These patients are all strongly positive.

So, it seems to me it would be very valuable to compare your new test to the established tests that have been around a while and are pretty reliable.

Then, I think you have to raise a question about any extra positives they pick up because again, even if they were more sensitive, they really shouldn't be picking up any more natural infections. Where you would pick up the extras would be in vaccinees or in titration studies. So, that would be my recommendation for how to establish performance.

As far as whether they are needed, I don't think there is any call from like CDC recommendations, and so they might be needed in the future, but right now there is not much call for them. Testing people after vaccination to see if they have antibody is not recommended.

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DR. THRUPP: But it would be in the course of studies of vaccines pre-market.

Dr. Hollinger, did you have a comment?

DR. HOLLINGER: John, you are also talking here, you mention someplace in here I think about HAV RNA testing, which I don't see a great deal of use at this time, but I would agree with Jay that the tests for total antibody or immunity and vaccine response, and for IgM anti-HAV for acute disease, how long they have it and when they lose it, it is not critical, and I would think that that is the kind of testing that you would want to include in terms of evaluating new assays.

There probably is some qualitative differences in the antibodies during acute disease and also during the vaccination that may not be useful. If you don't feel that you need the anti-HAV test post-vaccination, then, it doesn't matter if there are qualitative differences in the antibody response at least initially. Later on, the total antibody would work quite adequately.

DR. HOOFNAGLE: What about this issue of new vaccines and addressing their relative efficacy?

DR. HOLLINGER: What do you mean, Jay?

DR. TICEHURST: You mean their immunogenicity?

DR. HOOFNAGLE: Immunogenicity of new vaccines.

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DR. HOLLINGER: I have been confused by the vaccine literature in hepatitis A, because it is often not clear what tests they are using to detect anti-HAV in vaccine recipients.

DR. TICEHURST: I can tell you.

DR. HOLLINGER: Okay. And does it still apply to our current test for anti-HAV?

DR. TICEHURST: To my understanding, the tests that have been used are as follows. There is two licensed vaccines now. One is produced by SmithKline Beecham, and for their studies, they developed their own EIA, and they used as a yardstick this WHO reference prep that I referred to.

If I remember correctly, their cutoff is 20 million IU/mL, so they considered anything above 20 a response, so if you read the papers and their literature, when they refer to responses, they are talking about 20.

The other licensed vaccine is a product of Merck & Company, and my understanding of the assay they use there was that they took a commercially available total anti-HAV assay and changed the configuration of it, so that was basically a home brew assay. The standard version of that assay calls for taking, if I remember correctly, 10 microliters of serum and diluting it up to 210 microliters.

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What they do is alter the proportions of the test serum and the diluent, so they get a more sensitive assay.

DR. HOLLINGER: I think instead of 10 and 100, I think they used 100 and 100.

DR. TICEHURST: Something like that, so that these represent home brew assays in essence.

DR. HOLLINGER: And there are other ways of doing it. I mean all of us experiment around it. The other way, of course, you just add the sample to the bead first and let it incubate overnight, and then come back with our detector system the next day. That improves sensitivity probably 10- to 50-fold by just doing that. So, there are ways to enhance the sensitivity of the assay. That is still a commercial assay. But that doesn't get to the issue of what you want to use it for.

I think that issue about--and Jay has brought up a very important point--that almost all of these vaccine studies have been in-house studies, by SmithKline on their Havrix, and Merck's Vagta, the in-house assay, and so there hasn't been a lot of experience outside of that to validate what you are going to do in terms of response, and the issues that we have with hepatitis B does not seem to be quite as controversial, if you will. With hepatitis A, it is like, well, you get the vaccine and we think you are

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protected, and we feel you are protected, and we are going to be happy with that, because it is not, quote "as serious a disease" perhaps as the other, or have at least the emotional impact.

DR. HOOFNAGLE: I guess the issue is whether the FDA, the vaccine, CBER I guess, would accept a new vaccine where they use the currently commercial assay adapted in that way to make it more sensitive. It seems like they used it once, they can use it again.

I assume the reason why the company doesn't change to that configuration is that you have a higher false positive rate.

DR. TICEHURST: May I?

DR. THRUPP: Yes, please.

DR. TICEHURST: We have gotten inquiries from companies who would like to market very sensitive assays for anti-HAV in this country, and the question really becomes if there is no indication at this point for high sensitivity, what do we allow them to put in their package insert.

They want to say--and I have been told this by a company representative--that it gives them a marketing advantage to say that their assay is more sensitive. We are inclined to say fine, you may have a more sensitive assay, but since there is no indication for that greater analytic

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sensitivity, there is no reason to say that in the package insert.

DR. HOOFNAGLE: In fact, again, you are trading off specificity, which here would be much more important.

DR. TICEHURST: You raised the point before, you saw as a mainstay for testing a new assay would be to compare it to an old assay, and you are going to get some results from the new assay that are going to be positive when the old one is negative.

What do you do when you have the ultra-sensitive assay?

DR. HOLLINGER: Dr. Fields, you have had some experience, haven't you, with some quantitation of HAV? I don't know if you did this with some vaccines studies or what, but is that correct?

DR. THRUPP: Dr. Fields, if we could ask you to comment, please.

DR. FIELDS: Thank you very much. Yes, we, in fact, have finished a hepatitis A vaccine trial using SmithKline vaccine among Native Americans, and for that vaccine trial we used a licensed commercially available test that is available in Europe, not in the United States, and it is a quantitative assay with sensitivity down to 10 to 20, thereabouts. So, that is the experience that we have

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had. That study is in the process of being written up and published. It is not out yet.

Specifically, which question would you like for me to address?

DR. HOOFNAGLE: Is the current commercial assay available in the United States, do these people seroconvert by that assay?

DR. FIELDS: Some, not all. Certainly the more sensitive test is more useful for vaccine response, yes, because the antibody titers, as already stated, are not as high post-vaccination as they are following a natural acute infection. So, I think there is some utility for a more sensitive test as it applies to the post-vaccine setting.

DR. HOOFNAGLE: Evaluation of vaccines.

DR. FIELDS: Exactly.

DR. THRUPP: Dr. Fields, for the transcription, would you just mention your affiliation for the record?

DR. FIELDS: Yes. Centers for Disease Control, Hepatitis Branch, Centers for Disease Control and Prevention.

DR. THRUPP: Thank you.

I could recognize--I have forgotten your name, I am sorry.

DR. HOLLAND: Paul Holland from the Sacramento

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Blood Center. Actually, I would like to give you an example of how the testing with these home brew ultra-sensitive tests based upon the vaccine can be very misleading.

I was one of about 30 of my employees who recently took the hepatitis A vaccine. I was about to head for India, and I wanted to be protected. Just to find out for our own interest, we tested all the employees at several weeks and then one, two, and three months, and so on.

What we found is that only 50 percent of them had detectable antibody by the commercial assay that is available to us. I took this to mean that only 50 percent of the people were actually vaccinated.

DR. THRUPP: This is post-vaccination?

DR. HOLLAND: Post-vaccination. We wrote to the company and they never told us in the letters--and I have two letters from them--that their measurements were with the home brew ultra-sensitive assay. So, my presumption was that 50 percent of us, including myself, were not immunized. I still don't know whether I am or not until I find out with one of these ultra-sensitive assays.

But I think it is interesting that the vaccine was licensed using really non-licensed assays to verify the antibody was there, because the presumption was that you don't need to be tested. We happened to be tested, and I

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said my interpretation is half of the people including myself do not have immunity.

DR. THRUPP: This is reminiscent of the debate on ultra-sensitive versus standard PSA assays.

DR. HOLLINGER: It is true, though, Paul, that just by altering the regular commercial tests that are available, as I mentioned just a little while ago, either by the concentration or the serum added, and so on, that you do find that almost 95 percent or greater, close to 100 percent actually make antibodies, but you just have to alter it.

But doing it just regularly, the regular assay, you don't get that, so there would have to be some changes if you were going to use it, I think, if you are going to use it to determine whether a person is immune or not.

DR. HOOFNAGLE: But the studies have shown that people are immune even with these low levels of antibody, so I think it is just going to lead to confusion unless they can come in with these assays and show that they are just as specific as the current assay, that they do as well with natural infection, and don't pick up a bunch of false positives.

DR. THRUPP: We are coming down to focusing on what is the appropriate predicate to assay and what can the FDA do to establish such.

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DR. HOOFNAGLE: What does predicate mean?

DR. THRUPP: Dr. Gutman.

DR. GUTMAN: Predicate would be a legally marketed device. That could be one that was on the market at the time that the '76 law was passed. It could be one that fit into a classification developed by a classification panel, a number of panels met in the late seventies or early eighties or it could be frankly a device that has been brought to market that is, in fact, linked to one of those products.

DR. THRUPP: Dr. Gutman, how would you suggest the panel respond to this question as to what should be done to establish--it sounds like there is a need in the vaccine studies for a high-sensitivity assay--

DR. GUTMAN: I was actually hoping you would tell us. I wasn't actually going to provide the answer to you.

DR. THRUPP: I think the discussion is going that way, that there is a need in vaccine studies for a high-sensitivity assay. Perhaps we can't say more than that at the moment.

DR. GUTMAN: I guess I am not connecting that. I mean obviously, if there is a high-sensitivity assay and the predicates are not high-sensitivity assays, one has to find some standard against which to measure the increased sensitivity. The panel yesterday wasn't very enthusiastic

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about discrepancy resolution, but one begs for some mechanism for understanding what the truth is when there are differences.

The issue with this particular analyte, actually, you have confused me by the notion of predicate because the notion is that the assays have been around so long, the disease is established so well, the conventional assays are well established, and it might be hidden somewhere in the context of the many background questions, is the notion that not for an ultra-sensitive, because that is frankly not intended use, but maybe for a nonultra-sensitive, just for the next improved version of the antibody test, maybe we could, in fact, take the predicate and take some modest clinical data, in fact, develop a mechanism for bringing it to market.

There is an even more interesting subtext, which is maybe the assay should be down-classified from a Class III. We are really keeping this scientifically focused, but I don't have any aces up my sleeve in terms of some kind of nucleic acid amplification test for knowing the truth about the HAV immune status. John, help me out.

DR. THRUPP: What we have really gone on to is the first part of the questions that are on the right of your screen, which is should the Center use an approach that

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emphasizes the very high analytical sensitivity, and should there be comparison of new and--well, there isn't really high sensitive--but previously licensed assays, which are the standard one, by testing large numbers of single specimens.

DR. HOLLINGER: For regular infection, I mean if you are just looking at infection and immunity, the current assays are very good. Dr. Ticehurst has mentioned that their antibody levels are very high.

I remember we did a study in Greenland many years ago where we used regular commercial assays and even after 25, 30 years, I think, in that particular population, the patients were still antibody positive, so I have no concerns at all about the current assays for detecting immunity, nor do I have any concerns at all about acute infection. I think the IgM assay is an excellent assay and the total antibody is also.

It only comes to a question about whether you really need to do post-vaccination testing and whether that is important. If you make that assumption, then, of course, one way of reviewing that would be to evaluate assays in people who have been vaccinated.

You are vaccinated, you draw their blood at a few periods of time there, and then you compare them in parallel

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testing with the currently available assays and determine whether that is useful, and allow them then to make statements in their product sheet, comments about where they can detect the antibody, at what level, and so on, and whether it's important, perhaps even after the two shots are administered. Then, I think it would be useful without looking at concentrations, just positive or negative.

I think that would be a relatively easy way of determining sensitivity of these assays.

DR. THRUPP: I think you just answered the second and third questions there with yes's and under these circumstances for the vaccine studies, are serially collected specimens necessary and are new studies essential in the development of a vaccine, I think the answer was given yes.

Paul.

DR. EDELSTEIN: If the clinical indication for this new assay is to determine immunity, then, I think the only way you could establish that is by doing a clinical trial that correlates the results of the assay with immunity would be a huge study, because otherwise how could you determine what the specificity of your assay was, and that I think is the real issue.

I suppose you could use a surrogate marker of

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testing before and after vaccination, but it is possible that just the active vaccination alone might cause some false positive antibody response.

So, I think if the manufacturers want to market the tests for the indications of assessing immunity or a successful vaccination, then, they need to prove that clinical question. I don't think that simply doing parallel assays with the predicate devices is going to work because if these assays are more sensitive, you are going to have plenty of specimens that are positive when the predicate assay is negative and how then do you determine the specificity of that reaction.

It is not only the specificity of the antibody you are measuring, but also whether those people will be immune.

DR. THRUPP: Well, the documentation and the assessment of the assays serially would be what Dr. Hollinger was referring to, but you are raising the second question that the nitty-gritty of the clinical efficacy, which is obviously related but it's a separate extension of studies.

Could someone just comment briefly on what populations were used for the currently licensed hepatitis A vaccines for the efficacy studies?

DR. TICEHURST: I can answer that if you want.

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DR. THRUPP: Dr. Ticehurst.

DR. TICEHURST: The main efficacy study for the SmithKline Beecham's vaccine was done in approximately 40,000 children in Thailand, in remote areas of Thailand where there was a high incidence of hepatitis A, and the efficacy study for the Merck vaccine was done in an isolated community on the Hudson River in New York. It was a particular type of Jewish community where they had a high incidence of hepatitis A infection. They actually broke the code in that study.

DR. THRUPP: So, in answer to your question, Paul, obviously, it would appear that populations are going to have to be found for a new candidate vaccine in which it can still be studied.

DR. EDELSTEIN: There are plenty of places in the world where you can find very high attack rates of any of the hepatitis viruses we have talked about, so that shouldn't be a particular impediment.

DR. THRUPP: Dr. Gates.

DR. GATES: What we were originally talking about is in the context of having a test approve the efficacy of a vaccine, and it seems like we are going the other way. I mean borrowing a page from susceptibility testing the way you get Kirby-Bower zone sizes by having the drug companies

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do the testing for the antibiotic and bring it over to the device side, and this seems like a similar issue. From the efficacy for tests like this based on designing the vaccine, then, use that data to establish it as a diagnostic test.

DR. EDELSTEIN: But in this sort of a study, you are not determining the efficacy of the vaccine, you are determining the efficacy of the test that determines whether a patient is immune. Whether they respond to the vaccine or not is irrelevant other than for the purposes of designing the study.

DR. GATES: Other than they developed a test that allowed them to do that in these cases, and presumably validated that test, and confirmed it based on all the studies they did that it worked properly, so I don't know. It's kind of the horse and the cart here.

DR. THRUPP: Well, you are probably considering the horse and the cart together in the studies in parallel, in the properly designed study.

Dr. Specter.

DR. SPECTER: It seems to me that we have already heard statements that in establishing the efficacy of certain vaccines already, we have taken a predicate test and modified it to a level where it was considered acceptable for assessing this vaccine that has been approved by the

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FDA, so it would seem like it would be reasonable to use that modification, which apparently is published, as a comparative.

Even though it is not an FDA-approved test, it is one that was utilized for an FDA-approved product, so it seems like it is an acceptable way to go, and that would make a reasonable standard to compare these highly sensitive assays.

DR. EDELSTEIN: As long as you knew the performance characteristics of the test that was used.

DR. SPECTER: Well, I make the presumption that this was an approved vaccine, that those performance characteristics were presented with this vaccine trial.

DR. THRUPP: Dr. Ng.

DR. NG: I just simply want to reiterate I think Paul and I are in agreement. You can make an antigen, you can shoot it in somebody and show they make an antibody against that antigen, but you don't know from that laboratory test that that person is protected from infection, and if you look on page 767 of Dr. Hollinger's chapter in the Fields' Virology Text, there is that Thailand study in there, and there were 2 children versus 31 in the post-surveillance period who had received the vaccine, but developed hepatitis A.

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So, a question, in that study, can you look up for those two individuals what was their serologic assay on their modified test versus those 31, can you get some relative rate there to figure out how to interpret those ELISA values, for example?

But I see what we are discussing here, if you want to develop a test to make sure that you can develop antibodies against an antigen, sure, you develop a new test, but you have got to go through the whole clinical trial to show if that antibody test correlates to immunity. Those are two separate things.

DR. THRUPP: Well, the point Dr. Specter is making is that that has been done presumably in previous trials.

DR. HOOFNAGLE: No. They showed the vaccine was immunogenic, but then they also showed the vaccine was effective, but those things weren't necessarily correlated. The vaccine was effective, but they have not correlated the effectiveness of vaccine with how immunogenic it was, unlike in hepatitis B where there is some data that less than 10 IU is not protective, it is not real solid data, but it's pretty good data. In hepatitis A, that hasn't been established yet, has it?

DR. THRUPP: So, your point would come back full circle.

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DR. HOOFNAGLE: I would come back that the only use of this test is to evaluate new vaccines, and if the FDA is willing to look at modifications of assays, I don't see a need for a new licensed assay as a diagnostic.

DR. HOLLINGER: But, Jay, let me ask a question here I guess. First of all, I agree, I think the vaccine is good and protective, but a lot of patients want to see a number that says that they have been protected, quote "protected," and so you give them the vaccine and after their two doses, you now test them and they don't have any antibodies.

DR. HOOFNAGLE: There is no government agency that is recommending that you do that.

DR. HOLLINGER: I know.

DR. HOOFNAGLE: So, just go to the lab and modify the assay and say here is the number. But the FDA shouldn't have to go around regulating the world to stop you from doing that.

DR. THRUPP: Could I ask Dr. Fields to comment once more?

DR. FIELDS: Thank you. Let's understand that this 10 MIU or 20 MIU level that afford protection is based on the current sensitivity of the available test. In fact, we don't know what the level MIU value would be that affords

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protection. It may be much lower than that.

DR. HOOFNAGLE: In what disease?

DR. FIELDS: Hepatitis A. We know about hepatitis B, that is for sure. Unlike hepatitis B, we don't know what level of circulating antibody affords protection. It is strictly based on the available test that we have right now.

DR. HOLLINGER: Along that same line, when the immunoglobulin was given, you rarely could detect it in the bloodstream, yet we know that the vast majority of these patients, 80 percent, maybe even 90 percent of them are protected against getting hepatitis A.

DR. FIELDS: But that was still using--

DR. HOLLINGER: With undetectable anti-HAV.

DR. FIELDS: But that was still using the licensed test in the United States.

DR. HOLLINGER: That is what I am talking about.

DR. THRUPP: Dr. Charache.

DR. CHARACHE: I just didn't want to prejudge that because one branch of the FDA used a given test, that it meant that the Devices Branch had evaluated it, so I think the fact that Dr. Specter was commenting that the FDA had already used it, doesn't mean that it was necessarily the kind of thing one would market for general use.

DR. SPECTER: We are not talking about marketing

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it for general use. We are talking about using it as a standard to see if a test is effective by comparison for detecting immunity.

DR. CHARACHE: But I don't know that it has been standardized to a point that one could use it as a predicate.

DR. GUTMAN: But that would be the issue to be answered in the same way as we talked about when we were talking about the nucleic acid amplification.

DR. CHARACHE: Exactly.

DR. GUTMAN: If the data does exist to support that performance, then it might, in fact, be a reference against which an ultra-sensitive assay could be evaluated, but it would depend on what the data shows.

DR. HOLLINGER: So, John, I think in any new test I guess that came up, I guess one of the ways in evaluating would be to do parallel testing, forget the vaccine and this other one, but to do parallel testing on a variety of samples, immune patients, if they have acute patients that come in, and so on, acute samples, and so on, and see if they are comparable and if the false positive rate is acceptable. I presume that is what you would consider or not consider.

DR. TICEHURST: May I respond to a couple things?

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DR. THRUPP: Dr. Ticehurst.

DR. TICEHURST: Just to put the ultra-sensitive issue perhaps to rest for the next year or whatever, I think there are data from which I would conclude that the kinds of configurations that were made in the vaccine studies, and keep in mind--somebody said this before, Dr. Ng said it-- just because there is an immune response to the antigen doesn't mean there is protection.

The data support that those responses that were detected by those reconfigured assays or the home brew assay do not necessarily correlate with protection. Dr. Fields or somebody can correct me if I am wrong. If I remember correctly, the data that were cited in the ACIP recommendations said that although about 95 percent of people had a detectable response by one of these ultra-sensitive assays within two weeks of their first dose of vaccine, only about 60 percent had detectable neutralizing antibodies to the virus. That is usually what most people accept as the criterion for immunity, but it is not a practical reference point.

If we wanted to study this kind of thing, the type of study that Tom Simms in our branch suggested was one I referred to earlier, and it has been alluded to, there are lots of people that get immune globulin, and as Dr.

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Hollinger said, they are known the vast majority of time to be protected, but have very, very low levels of antibody, and there are studies that have quantified that antibody by whatever means. Those are the kinds of people that could be used for validating a cutoff, if that were the case, but it is not an easy study to do.

With regard to the issue about doing the comparative studies, I may not express this well, but it is something that strikes--it is not the typical sort of study that we expect for a Class III device. Again, it depends on the indication.

If the indication is to detect evidence of a past infection, whether for the purpose of pre-vaccination susceptibility or as an exclusionary diagnostic, it is not typically what we expect of a Class III device. That doesn't mean it is not scientifically appropriate, but I just wanted to throw that out.

Keep in mind that the stuff that was discussed at the very beginning of the day, the way we regard these assays and the concern, the risk, not the risk of the device, but the risk of false results leading to misdiagnosis, and that is the thing to consider. I will have to think about that or we should all think about that, if comparative testing for total anti-HAV would allay any

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concerns about the implications of false results for total anti-HAV assay.

One thing to keep in mind, as a number of people pointed out to me, a lot of laboratories traditionally have used the total anti-HAV assay as a first-step assay before they do an IgM anti-HAV assay. There is an assumption there that the assay has a very high negative predictive value, and I don't know, the fact that it is often--that is not in any package insert, it is sort of a laboratory practice, sort of an off-label use as it were--if that frequent use would lead you to reconsider what you said.

DR. HOLLINGER: Basically, I think the reason that that is done is that the total antibody test is a very short test, it's a day test, so you can do it, if it's positive, then, you can put your IgM test on, which is an overnight test, and it saves money because many of them are going to be negative.

I think, John, that is the reason why, and it makes sense, because all IgM antibody-positive tests are going to be total antibody-positive, so if you do the total antibody and it is negative, not essential to go ahead then with the IgM test, and the vast majority are going to be that way. So, I think that was probably the reason, a good reason why that is done. I think economically, it makes

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sense.

DR. TICEHURST: But you are assuming that the negative predictive value of that first assay is very high.

DR. HOLLINGER: Yes, I am assuming that, yes.

DR. SPECTER: That is the point that was made earlier, John, there is not a problem with sensitivity in infection, it is really with vaccination, so the concerns about infection in a highly sensitive test don't seem to be warranted.

DR. THRUPP: Some aspects of the last question there have been perhaps alluded to at least. If new studies are essential, when should they be performed, pre-market or post-market?

DR. CHARACHE: That is awfully hard to answer in abstract. Almost certainly the answer is both as many post-market as are safe, as many pre-market as are required.

DR. THRUPP: Are you running for governor?

DR. CHARACHE: Not in Maryland.

DR. THRUPP: I don't see a lot of hands up to try to give a more definitive answer than Pat's. I don't think we are going to get any more answers there.

Are there any more questions on the hepatitis A issue before we open for industry and public response on any of the topics for the day?

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No more hepatitis A. Okay. Then, let's reopen the session, on which we have already had some comments on hepatitis A, from those in the audience, but does anybody else want to ask any questions or enter any comments about A, B, or C? Dr. Fields, CDC.

### **Industry and Public Response**

DR. FIELDS: Thank you. I would like to make a few comments about the test for detection of genomes, namely, polymerase chain reaction. There has been a lot of discussion about PCR and its utility, with regard to sensitivity and specificity, as well.

I remember our esteemed colleague, who is not here, Dr. Bob Purcell, I remember a presentation that he once gave during he showed two consecutive slides. One was advantages of PCR, and it said sensitivity and specificity. The very next slide was disadvantages of PCR, and it was also sensitivity and specificity. I think that is very, very true.

I would like to point out that PCR, by its very nature, is highly specific. It is intrinsically specific because it relies on hybridization, which is probably a lot more specific than an antigen antibody reaction.

So, I would argue then that the specificity problem surrounding PCR is not intrinsic to the technique

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itself, but it rather speaks to specimen processing and probably, to a much larger extent, laboratory environment.

I think Roche has done a very good job addressing these issues by the inclusion of UTP and downstream treatment with UDG to prevent contamination. My question to FDA is whether or not it would be in the purview of their organization when looking at licensing PCR tests, whether they would take into consideration the laboratory in which these tests are being done, the configuration of the laboratory in which they are being done, because I think that is the major issue with regard to the amplification assays.

DR. TICEHURST: Can I respond to that?

DR. THRUPP: Dr. Ticehurst?

DR. TICEHURST: Ms. Poole said I couldn't respond.

MS. POOLE: We will take that into consideration, Dr. Fields. Thank you.

DR. HOOFNAGLE: I didn't actually understand what you were saying. What do you mean? Of course, they take everything into consideration.

DR. FIELDS: Do they?

DR. HOOFNAGLE: You mean the extra steps to ensure lack of contamination?

DR. FIELDS: That is right, the laboratory in

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which the assay is being done. FDA, I know controls the safety and efficacy and effectiveness of the assay itself, but the problem with PCR and these other amplifications, not signal amplification, but target amplification procedure is in specimen processing and laboratory containment.

DR. HOOFNAGLE: I agree.

DR. FIELDS: That is what I mean.

DR. HOOFNAGLE: That is what I meant by stressing that the FDA should assess how the test operates in the field, not just in your laboratory or in Roche's Central Laboratory, sent out to clinical laboratories, how it works, that is an important element.

DR. FIELDS: One only has to look at the data from the Euro-Hep panel.

DR. THRUPP: Dr. Zabransky.

DR. ZABRANSKY: When I started doing the RT-PCR, the Roche test, in my laboratory, they came in and, quote, "certified" my laboratory as dictated by FDA is my understanding. This was required. I am talking about HIV now, HIV viral load testing. This was dictated or told to them by FDA that we had to do this, and I think anybody that is doing the Roche test had to go through that, quote "certification" process which was given by the company.

DR. GUTMAN: I can make a couple of comments. For

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new technologies like nucleic acid amplification, we, as a routine for most new technologies, would be asking for site data. That is a mixed blessing because we don't choose the sites, the manufacturers do choose the sites, and you can lull yourself into a false sense of security thinking that three or four or five selected sites will extrapolate into all of America, but we do have some insight into site-to-site variation.

We do also have some ability when we have complex technologies to put recommendations for use based on that site experience. We can talk about running assays in different rooms and having trained operators and having educational programs or having certain types of quality control. I think this panel, in fact, was notorious for having dealt with quality control issues on nucleic acid amplification technique sometime in the last two or three years and had specific requirements which I presume ended up in package insert labeling.

Where we fall short is obviously we don't regulate labs, we leave that up to CLIA, and so the final step in assuring that the package inserts are being followed and that the certification programs are being followed is a little bit at the edge of our reach, but we do everything we can to understand lab tests in the best way we can and to

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communicate in the package insert the best way we can, and to try and ensure that the products are used appropriately, according to instructions. Sometimes we win and sometimes we lose.

DR. THRUPP: Do we have some other comments from industry or other interested observers? Yes, sir.

MR. WESOLOWSKI: My name is Alex Wesolowski. I am from Roche Molecular Systems. I am Senior Director of Regulatory and Clinical Affairs.

I would just like to address the issue about training. This panel, this very panel actually went approving our MTB tests approximately a year or so ago, did recommend that we institute a training program for new users of the test system, which we have done, and we do continue to do that to today. Dr. Zabransky is absolutely right. We also have a certification and training program for HIV tests and, in fact, as I think a reputable manufacturer, we have instituted training programs for all of our products. So, I believe we do effectively deal with that issue.

The training program deals not only with how to run the assay, but also how to set up the laboratory, and, in fact, all new operators are trained at a Roche site and then we have somebody go to the site where the testing will be done and talk about good PCR laboratory technique and

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separation of different parts of the assay, including specimen preparation, reagent preparation and amplification and detection.

DR. THRUPP: So, I am assuming that your response is indicative that the FDA recommendations that came out previously were helpful in your implementation of this.

MR. WESOLOWSKI: I think it is fair to say that we had a lot of fruitful conversation and discussion with FDA about how this technology should be handled and what needed to be done to educate and train people on how to use it properly.

DR. HOOFNAGLE: I have a question I guess to Roche about the standardization of your assay and the level of cutoff, basically quantitation. One of the concerns that we have had in the field is that the different companies that have come in with assays for quantification of both B and C, they have different standards, so that a Roche standard that is, say, 100,000, in another company's assay will be a million or something like that. How is this going to be resolved?

MR. WESOLOWSKI: Well, we would propose to work together with the agency and hopefully other members of industry to come to a consensus standard, so we are all calling apples "apples," and oranges "oranges."

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It is a little confusing right now if you look at the state of affairs with HIV, quantitative HIV testing, where our test is currently the only approved method, will give you one result, and perhaps you can get two- or three-fold different results with one of the other available methods.

I think long term we all want to move to an international standard. Unfortunately, the international standards have been slow in forthcoming. There is a group in England right now proposing the availability of an HCV material as an international standard. We are trying to work with them as closely as possible to ensure that development.

DR. THRUPP: From a regulatory or the FDA standpoint, Dr. Gutman, can you offer any insights into this real issue?

DR. GUTMAN: No, I think actually he has got it right, that we probably need to work with industry and with other government groups to try and help them standardize. It is not something that we are in a position to do on our own. It is certainly something that we are in a position to assist with, though we have got a pretty full plate right now, and I am not sure where it fits in our agenda. It is a really important issue.

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One is looking at the upper end of technology, but if you look from our division, we look at the low end of technology and see some horrifying lack of standardization at the other end, as well, so it is a thing that we haven't done particularly well historically and need to do better in the future. Maybe as we reengineer and reform, we will have energy and time to redirect in new ways.

DR. THRUPP: Are there any other comments from the audience? Are there any other suggestions or comments from the panel members?

DR. HOLLINGER: Just on what was said here with Roche. We, in the last year, did proficiency testing of five laboratories in this country for HIV of which Roche participated. I think it will be published in March.

Basically, what surprises or what pleases, I guess, the whole thing, in other words, there were 35 samples sent out, they were in duplicates, triplicates, et cetera. They were all the same grade, the most common one here in this country, and they were done under code by Roche, Chiron, NSBA, ligase chain, and our own assay, so there were five I think that were done, and what surprises is that four of the five actually came out very close in terms of numbers, extremely close on the numbers, that is, 100,000, they were very close right down the line on it, so

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that was an encouraging finding.

So, as I said, I think that the kits, regardless of where they are being manufactured and by whom, under the proper control, can lead to--and with the proper standards--can lead to comparable results in most cases.

DR. THRUPP: Was the fifth one a different setpoint because of some differences in the technology?

DR. HOLLINGER: We actually don't know, and they don't know the reasons, but they were about a log off with what everybody else was getting, and that is being looked at, but there has been no explanation for it.

DR. THRUPP: That helps the background, the background noise.

DR. HOOFNAGLE: This relates both to quantitative and qualitative tests, and the quantitative tests, of course, the titer, but also in the qualitative tests, what level are you detecting down to? It is actually critical to future studies of therapy.

DR. THRUPP: Any other comments?

Dr. Gutman, Dr. Ticehurst, are there any other questions that the FDA would like to throw out?

MS. POOLE: Were there any questions that you feel you didn't get a response to, that you need a response?

DR. TICEHURST: What I would like to do, if I

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could, please, would be to run back through the questions that were presented at the beginning of the day, and maybe I can re-present those and summarize in terms of where we did get answers, and maybe reflect on where we didn't.

I have disconnected enough synapses by this point that I am not sure I can go through and give you a stock answer. With a five-minute break, I could do that if you want me to do that.

DR. GUTMAN: Why don't I suggest that we not do that. I think it has been a long day, and what I would suggest is that you take, particularly the general questions, home with you, and also the people in the industry or public or CDC take the questions home, and those of you who are very kind-hearted and don't mind giving the government a little extra time for whatever we are paying you, might actually try and summarize your thoughts based on the context of your colleagues here, and feed them back to Dr. Ticehurst in the next--well, I gave you 90 days, but if you got them back in a couple of weeks, we would be grateful.

Our intention is to interact with industry at this point and we won't leave you out of this interaction. I don't think we will have another formal panel meeting immediately, but whatever the fruits of our interaction will

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be, we will share with you, to have ongoing insight, and so you will have time to titer up or to titer down.

We are very anxious, we think there is a lot of really exciting new technology that needs to be out there to help you run labs and provide patient care, and the issue is it is really important to us to get it right. We don't want to get it too high, and we don't want to get it too low, we want to get it right. I am not sure I am going to ask John or you to pull it all together right now, that's not reasonable.

I personally want to thank you and particularly thank our Chair and thank John for the incredible work that you guys have done in keeping us moving and providing, not all the answers, but a lot of interesting insights.

DR. THRUPP: That is a nice closing comment. Thank you, Dr. Gutman, and if there is no other business, we can declare the meeting adjourned.

[Whereupon, the proceedings were recessed at 4:30 p.m., to reconvene on Friday, February 13, 1998, at 9:30 a.m.]

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