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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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HEMATOLOGY AND PATHOLOGY DEVICES PANEL

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July 18, 2008
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

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DOROTHY M. ADCOCK, M.D.	Chairperson
PIOTR KULESZA, M.D., Ph.D.	Voting Member
HELEN H. WANG, M.D., DR.P	Voting Member
BRIAN S. BULL, M.D.	Temporary Voting Member
JOHN A. KOEPKE, M.D.	Temporary Voting Member
GERALD J. KOST, M.D., Ph.D.	Temporary Voting Member
VALERIE NG, Ph.D., M.D.	Temporary Voting Member
DIANE H. NORBACK, M.D., Ph.D.	Temporary Voting Member
ANNE S. RICE, MT(ASCP)	Temporary Voting Member
LINDA M. SANDHAUS, M.S., M.D.	Temporary Voting Member
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DAN BRACCO	Industry Representative
LOUISE E. MAGRUDER	Executive Secretary

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RAY OSMOND

L. MICHAEL SNYDER, M.D., Chair, UMass Memorial Department of Hospital Laboratories

PAUL RUST, Vice President, Quest Diagnostics
Managing Director, HemoCue

GUEST SPEAKER

JUDY YOST, M.A., MT(ASCP)
Director, Division of Laboratory Services, Centers for Medicare and Medicare Services

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M E E T I N G

(8:07 a.m.)

DR. ADCOCK: Would everyone take their seats please.

I would like to call this meeting of the Hematology and Pathology Devices Panel to order.

I'm Dr. Dorothy Adcock, the Chairperson of this Panel. My area of expertise is homeostasis. I serve as the Laboratory and Medical Director of Esoterix Coagulation, and I'm a pathologist.

Ms. Magruder, the Executive Secretary for the Hematology and Pathology Devices Panel, will make some introductory remarks.

MS. MAGRUDER: Good morning. I will read the Conflict of Interest Statement for this meeting. FDA Conflict of Interest Disclosure Statement (Particular Matters of General Applicability). Hematology and Pathology Devices Panel of the Medical Devices Advisory Committee, July 18, 2008.

The Food and Drug Administration is convening today's meeting of the Hematology and Pathology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members

and consultants of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. paragraph 208 and paragraph 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. paragraph 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under paragraph 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of the 18 U.S.C. paragraph 208, their employers. These interests may include investments, consulting, expert testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion of issues relevant to the potential for automated differential cell counters being waived under the Clinical Laboratory Improvement Amendments. This is a particular matters meeting of general applicability.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) and paragraph 712 of the FD&C Act, to Dr. Dorothy Adcock. Dr. Adcock's waivers address a speaking interest with a firm at issue. She received less than $5,001 for this involvement, which is

unrelated to today's agenda. These waivers allow Dr. Adcock to participate fully in today's deliberations. FDA's reason for issuing the waivers are described in the waiver documents which are posted on FDA's website at www.fda.gov.

Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dan Bracco is serving as the industry representative, acting on behalf of all related industry, and is employed by Oxford Immunotech.

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

FDA encourages all other participants to advise the Panel of any financial relationships that

they may have with any firms at issue.

Now, I'd like to make a few general announcements.

If you haven't already done so, please sign the attendance sheets that are at the registration tables by the door.

The transcripts of today's meeting will be available from Free State Court Reporting, Inc., and their telephone number is 410-974-0947.

Information on purchasing videos of today's meeting can be found on the table outside of the meeting room.

I would like to remind everybody that members of the public and the press are not permitted beyond the panel area which is the area beyond the speaker's podium.

The press contact for today's meeting is Karen Riley. Karen, would you please stand? Karen may not be here yet. We might get an opportunity to point her out later.

I would like to request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the open public hearing session today and have not previously

provided an electronic copy of your slide presentation to the FDA, please arrange to do that with AnnMarie Williams. Is AnnMarie in the room? She's outside at the registration desk.

I'd also like to ask you to please silence your cell phones at this time.

Today FDA will be seeking Panel input on whether the CBC with differential counter is a reasonable candidate for waiver, and if so, what studies and what performance would be appropriate to demonstrate that the test should be waived.

Deliberations of this committee will be presented at the September meeting of CLIAC to allow for discussion of the issue by that committee as well.

Following the open public hearing, FDA will be making four presentations to outline our general waiver review criteria and to describe how these criteria might apply specifically to the CBC with differential counter. Following FDA, CMS will provide perspectives from the CLIA program. The rest of the day will be devoted to Panel discussions.

Dr. Adcock.

DR. ADCOCK: Thank you, Ms. Magruder.

At this meeting, the Panel will discuss and

make recommendations on issues relevant to the potential for Clinical Laboratory Improvement Amendments waiver of automated differential cell counters. The Panel discussion will include pre-analytical, analytical, and post-analytical issues associated with performing the automated hematology complete blood counts, CBC, and differentials in a waived setting.

Before we begin, I'd like to ask our Panel members and FDA staff seated at the table to introduce themselves. As you do, please state your name, your area of expertise, your position and affiliation. We'll begin with Dr. Aziz.

DR. AZIZ: Good morning. My name is Hassan Aziz. I'm head of the Medical Technology Department at Armstrong Atlantic State University. My background is medical pathology, I've been a -- tech, and then I joined the educational venue in the education sense for the last 5, 10 years.

MR. BRACCO: My name is Dan Bracco, and I'm Vice President of Regulatory and Clinical Affairs with Oxford Immunotech. My area of expertise is quality clinical and regulatory, and I'm the Industry Rep.

DR. NORBACK: My name is Diane Norback.

I'm a faculty member at the University of Wisconsin and a hematopathologist.

DR. KULESZA: My name is Piotr Kulesza. I'm an Assistant Professor of Pathology at the University of Alabama at Birmingham. My area of expertise is cytopathology and molecular testing.

DR. SANDHAUS: My name is Linda Sandhaus. I am a pathologist. I'm the Director of the Hematology Laboratory and of Point-of-Care Testing at University Hospitals of Cleveland.

DR. KOST: Good morning. I'm Gerry Kost. I'm a Professor of Pathology and Laboratory Medicine at the University of California Davis, and my area of expertise is point-of-care testing.

MS. MAGRUDER: I'm Louise Magruder, and I'm the Executive Secretary of the Hematology and Pathology Devices Panel.

DR. NG: Good morning. I'm Valerie Ng. I'm Professor Emeritus from the Department of Laboratory Medicine at the University of California San Francisco. I'm currently Chair of the Department of Pathology and Laboratory Medicine at Alameda County Medical Center. I'm a generalist, laboratory medicine practitioner with expertise in point of care.

DR. WANG: I'm Helen Wang. I'm an Associate Professor in Pathology at Harvard Medical School and Medical Director of Cytopathology at Beth Israel Deaconess Medical Center. My area of expertise is obviously cytopathology, GI pathology, and epidemiology.

MS. RICE: Anne Rice. I'm a research biologist at CDC in the division Blood Disorders and Coagulation Lab. Previous to that, I spent two years as a surveyor for the State of Georgia in CLIA.

DR. BULL: Good morning. My name is Brian Bull. I'm Professor and Chair of the Department of Pathology at Medical School, Loma Linda University in Loma Linda, California. I'm a hematopathologist, and my area of interest is tests and measurements, statistics and hematology testing in general.

DR. GUTMAN: I'm Steve Gutman. I'm a pathologist. I'm Director of the Office of In Vitro Diagnostics, the workgroup that is hosting this event.

DR. ADCOCK: Thank you. We will now proceed with the open public hearing. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The Panel will be given an opportunity to ask questions of the public presenters at the conclusion of the open public hearing. If recognized

by a Panel member, please approach the podium to answer questions.

I would like to remind public observers at this time that public attendees may not participate except at the specific request of the Chair.

We have three requests to speak.

The first speaker will be Mr. Ray Osmond. Mr. Osmond, please come to the microphone.

MR. OSMOND: This one?

DR. ADCOCK: Yes, sir. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

MR. OSMOND: Good morning, Dr. Adcock, Panel members, and Mrs. Magruder. I have no financial interest in any company. I have paid my way up here myself, and I speak today as a consumer with the best interest of patient safety and am asking this Panel to recommend no to the proposal of the FDA to bring waiver status to the hematology automated differential counter.

As a medical technologist for almost 50 years, and as a laboratory consultant and physician office for the last 10, I think that I have firsthand, ground-level knowledge of the user or the

potential user of this equipment.

My waived laboratory personnel at this time have a great deal of problems with the present waived testing, much less saddling them with new intricate, difficult testing procedures of any kind at this point in time.

The CLIA was signed into law in 1988 because of the high incidence of laboratory errors or perceived high incidence of laboratory errors.

In this law, the CLIA was divided into three categories, high complexity, marked complexity and waived. The waived tests were defined as those that employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible or impose no reasonable risk if the tests were performed incorrectly. Let me repeat, simple and that if it is performed incorrectly, it will cause no harm.

The waived test category requires no personnel standards, minimal or no quality control practices, no expert or proficiency testing, and minimal inspections from outside agencies.

The Certificate of Waiver requires a license, a director, training of personnel, a procedure manual and to follow manufacturer's

directions. In these manufacturer's directions, it does not say that you have to or are required to perform quality control. You're not required to perform quality control in many of the waived tests now on the market.

I'm not anti-technology nor am I an advocate of strict restriction of elimination of process of patient testing and for the clinical decision making of the physician. I support aiding physician community access, these emerging technologies where they can be shown to provide real-time information but not at the expense of quality assurance and quality control.

This issue that is before you is not about patient care. It is strictly about money. This hematology equipment is not new technology. It is not something earthshaking that we have to save the world with at this point in time. It's been around for 20 years. The cell counter has been around for 50 years.

Now, if you do decide to approve this request by FDA, there are several things that you will accomplish. You will definitely increase the stock pay of the hematology companies present or to be present. You will definitely have an impact in

physician errors in the laboratory market because of all of the new, untrained people who are going to be saddled with this equipment, and the third thing is that the present users of hematology equipment will opt out of proficiency testing and will opt out of being inspected by any agency, outside agency, or the majority of them.

What this means is that quality and accuracy and reliability that is now in place will definitely be eroded away.

I have three studies that I've brought here that speaks to the user. One of them is the Good Laboratory Practices from CDC, and the other one is a CMS study done in 2003, and the third one is the newest report out by the Lewin Group that just came out in May.

The CDC study with a time period of 2000-2003 raised a number of questions concerning quality of waived area that had potential for poor patient outcomes. These studies, in particular, CMS and CDC study determined that quality deficits will most likely result in a high level of staff turnover at these locations, inadequate training, as well as clear lack of understanding of good laboratory practices and basic scientific knowledge by the user.

This study was done before the barrage of new laboratory tests approved by the FDA since 2004.

Since 2004, there have been at least 50 to 75 new waived tests added that can be used which means that there's probably over 100 analytes out there that are waived with very little quality control or quality assurance. This means that there are probably about 2500 systems out there available to the physician. This study went on to say that as many as 60,000 laboratories may not be following manufacturer's instructions and may consequently be performing tests incorrectly with potential harm to the patient.

The report went on to say that 77 percent of the 175,000 laboratories have no direct oversight. Twenty percent were not performing quality control as required by the manufacturer. An additional 12 percent were not performing QC as required by CLIA. This is before anyone introduced new tests.

Before you make a decision, I hope that you will ask the FDA to prove simple and hazardous analysis. I want the FDA to prove that they have studies in place that takes the user -- and we're talking about a user who is not a medical technologist. We're talking about a lay worker in

the office that gives shots, admits patients, and is going to do CBCs. I have trouble with this. I have a great deal of trouble with this type of user.

I have four of these pieces of equipment, hematology equipment in my offices at this point in time. They're not waived laboratory tests. These are moderately complex. We're talking about medical technologists and medical technicians. We turn out very good work. I have no problems with the present hematology equipment at all.

So what I have problems with is required quality control. Once these instruments are approved, I'd like to see where the required quality control is and what it is and that they would not change the required quality control with the new generations that has happened so often with new generations of tests. All of a sudden they had quality control, and the new generations have no quality control. They have something called EQC, whatever the heck that means.

In my own practice, with all of the new procedures and new kits coming in from China, I have trouble with no quality control being performed by anyone in a physician office. So I don't know how in the world with all the new things that are coming

out, that we could reassure a liability in the future.

I hope that this Panel will recommend that they not go forward with the proposal at all on the application of the CDC as a hematology, as a waived test.

I further hope that that this Panel will recommend to the FDA that they convene a panel of stakeholders that will examine this waived craze that at this time is out of control and is spiraling downhill, that the physicians and patients or the end user and safety is not one of the main requirements of the FDA at this point in time. They seem to have the bias of big business at their heart. What I'm asking is that we level the playing field, and it's not incompatible, the interest of big business and the patient, but patient safety should be the utmost concern of the FDA and of this Panel. Thank you very much.

DR. ADCOCK: Thank you. The next speaker will be Dr. Michael Snyder. Please approach the podium.

DR. SNYDER: Good morning. My name is Dr. Michael Snyder. I'm Chairman of the Department of Hospital Labs at the UMass Memorial Medical Center

in Worcester. That's 50 miles west of Boston. I'm also a practicing hematologist, and I'm here basically to talk about how important this test is in a clinical situation.

Our laboratory performs approximately 14 million tests per year and is growing at a rate of 20 percent. Many of our physicians practice 150 miles from where we're located in Worcester. This creates a problem. The problem is that in order for us to maintain good quality and to help patients and help clinicians make adequate decisions about what to use as far as antibiotics, it's important that we have a test available immediately.

What happens is, except for doctors' offices where there's a physician's office lab, the results of the tests is sent to our lab. It takes approximately a day to two days to get the results back. Therefore, it's too late to help the physician make a decision about whether or not to use specific therapy particularly antibiotics.

The antibiotics is mostly used in patients who come in with a febrile illness, and oftentimes the clinician is faced with the dilemma whether to use the antibiotic or not. A test, for example, a white cell count and a granulocyte count would make a

major difference as far as informed ability to make that decision. For example, if a patient has a viral illness, the white count oftentimes is normal as is the granulocyte count. In the face of a bacteria, we have elevated white counts and we also have elevated granulocyte counts.

Most times what happens is the physician makes a decision, either based on pressure from the family or based on his last few cases, and will start the antibiotics. There are several times when two cases exist. In the literature in the United Kingdom, a general practitionist demonstrated that in 61 percent of the time, antibiotics were used without any previous laboratory information. When laboratory information was available, the clinician ordered antibiotics 30 percent of the time, a significant change. In Japan, a similar study also existed in the situation where 90 percent of the time patients would use antibiotics without prior laboratory information and only 62 percent.

What this is is it creates a major problem. One of the major problems in public health as decided by the CDC is the emergence of resistant anti-bacteria, and we think and probably know this more that antibiotic therapy is probably a major cause, at

least associated with the emergence of bacteria particularly MSRA, Methicillin-resistant Staph aureus. We know that emergent antibiotic resistance has caused significant morbidity, mortality and insignificant costs. It is a significant issue for public health in this country.

So, therefore, a test such as a clear waived test, which will offer the physician practicing in remote sites the ability to make an informed decision, will be very important.

Now, we also know that in order to have this type of ability, one has to have (1) a test which is very simple to perform and (2) is it has reliable and accurate data. We did a study with Chempaq, when we -- about two years ago, since we've been looking for a handheld device which will give us CBC. We looked at a company called Chempaq from Denmark at the ACC meeting. We're very impressed. We contacted them, and we asked them if they would come into our lab and perform a test side by side comparing Chempaq with the LH 750 which we have, which is basically the same type of methodology, and lo and behold, we studied 410 patients from different sites from chemotherapy, from primary care, from remote sites, and the correlations were significant.

This data was published in the Clinical Chem Lab in March of 2008 and is available. I have some. If anybody wants to see the data, I have a summary of the data itself.

We're now performing the same type of test using lay personnel, clerks, secretaries, et cetera, and we've now studied I would say close to 300 cases, and we're finding very similar results. In fact, even better, it's performed by lay personnel. So we think that, one, the simple aspect of this is met. Two, the fact that the accuracy is excellent because we're not talking about a three part diff which we think is comparable to any other part diff which stands, and we're able to compare it favorably to a five part diff. So we're very, very, very optimistic about this.

Now, there are risks as any test. For example, analytic, pre-analytic data or information is very important. I would say that in our laboratory, we have about one percent error and mostly coming from pre-analytic data, when that sample's coming into our lab, whether it's from our UM University Hospital or from remote sites. What happens is we have the courier, missing samples, freezing samples when you're not supposed to be,

mislabeling samples, short draws, et cetera. And we all know who've been involved in laboratory medicine that that's a significant problem.

With the point of care apparatus, much of that disappears and we know that it's simple because we've been able to show now that lay people in our offices can do this and very simply, and we get comparable results to when laboratory personnel run the instruments.

So we feel very confident about the fact that the apparatus is simple. What needs to be done is to assure that the test is accurate, and I think that's the most important thing is, are the results that they get, the clinician at the remote site, being able to make an informed decision, whether the decision to use antibiotics is appropriate or not.

Now, what's happening is that we find that that's the case. However, what we also need to have is some device where one can have flags, for example, abnormal cells, leukemic cells, et cetera, that the clinician will be alerted that there's something more than just the usual phenomena. And, two, that if there is a short draw, there are bubbles in the sample, that that will be noted, and essentially the machine will stop, shut off, and not perform the test

and the test has to be sent into the main lab.

In addition, there are standard setup. For example, results of white counts greater than 15,000 should be checked out in the main lab. Hematocrit below a certain level, 20, should also be checked out. So, therefore, there are built in, built in factors which will control the process.

As far as in the post-analytic, I think this is one of the most important parts. What if we have false positives? False positives is probably no better off than what we now are standardly doing in our end remote office practice, particularly in the pediatric population. It's been shown by the CDC that in situations where a child comes into a pediatric office, has fever, and has symptoms where we're not sure between viral illness versus bacterial illness, the physicians oftentimes will submit to pressure by the parents, and in 75 percent of the cases, antibiotics are started, and I can talk about my own grandchildren that happens, and I'm even on the other side forcing him saying, why don't you start antibiotics imperatively. And that's what clinicians make.

However, if they have the information available to them, for example, the results of the

CDC white count and the granulocyte count, the lymphocyte count, which was accurate and they could trust, they could then make an informed consent, and I think what you'll see is that the drop in the antibiotics will have a significant impact on the emergence of resistant bacteria.

So I think that's important for false negatives, and that's always the most important thing when we're dealing with laboratory data in clinical situations. Basically what happens in that situation, if the patient has a negative result, the physician accepts that data, does not prescribe antibiotics. The symptoms persist. Usually what happens is the patient and the doctor decide again to retest the patient, and most times you now will see available the results and decisions are made, informed decisions will be made.

So I think overall, the ability of a point-of-care test, which is simple and easy to do, is accurate or has governance aspects to it to inhibit, provide it from going further is very important.

So I'm here to address you both as a laboratorian and as a clinician to say that in an imperfect world and in an imperfect science as laboratorians, we try to maintain -- we're talking

about practicalities in practicing in a remote site and I have a significant relationship. We have 3,000 physicians who send work to us many as far as 150 miles away.

DR. ADCOCK: Will you please conclude.

DR. SNYDER: Pardon.

DR. ADCOCK: Can you please bring it to a conclusion.

DR. SNYDER: Yeah, I am.

DR. ADCOCK: Thank you.

DR. SNYDER: So that if we are able to provide a service which gives them the ability to make a wise decision clinically, I think this will have a major positive impact in patient care and the decrease in the emergence of resistant bacteria. Thank you.

If anyone wants to see the data, we have a summary of 410 cases comparing venous and finger sticks both by medical technologists and by lay users. So it's here for everybody to view. Thank you.

DR. ADCOCK: Our next speaker is Mr. Paul Rust.

MR. RUST: Good morning, esteemed members of the expert Panel. My name is Paul Rust. I'm the

Vice President of Quest Diagnostics and also the Managing Director of HemoCue, our point-of-care testing subsidiary.

I'm here because our evaluator or pediatrician couldn't be here to present this information to you, but I'm mostly here to present the perspective of point-of-care testing from the perspective of Quest Diagnostics, a reference laboratory company.

I've been in the in vitro diagnostic business since 1970 and actually marketed point-of-care products back when Richard Nixon was in the White House. I marketed physician office complete blood counters in the mid-seventies, long before CLIA in 1988 was a reality, and I spent many years involved with the Hematrak differential cell counter, which many of you may remember is the size of this table, a device now that can be done with a handheld device, the results of which can be gotten with a handheld device. So I'm telling you this not because I want you to feel sorry for me because I'm so old, but to indicate that I have a unique perspective that comes from my experience in the many years in the business.

I've also managed laboratories for Quest

Diagnostics in New York and in California. So I have experience with the pre-analytic, analytic, and post-analytic processes, and I echo the description of the things that can go wrong that Dr. Snyder indicated at UMass.

Quest Diagnostics is the nation's largest reference laboratory with 24 major labs around the country, 2,000 patient service centers, 150 stat labs, and we treat 150 million patients per year.

Several years ago we recognized the opportunity, dramatic growth possibilities because of new technology, to bring choice to physicians that is not available today when a reference lab is the only possibility. So what interested most was this possibility of giving physicians a choice to choose between an overnight test when appropriate and a point-of-care test when appropriate. We're aware that patients have unique needs. Some come to the office via public transportation. Some bring a translator with them. That translator is not available when the results are available later. That patient may not be available to the physician to provide feedback much as they can with a point-of-care test. So there are advantages to having point-of-care tests for some patients, some of the time.

We don't think that point-of-care tests should replace central lab testing all of the time, but to Dr. Snyder's point, in remote locations or in locations where the patient result cannot be gotten to the patient quickly or where the benefit of that hugely important physician/patient interaction can take place in the point-of-care setting provides a unique opportunity.

So making lab tests available to reach the maximum number of patients requires access through CLIA-waived labs in our view.

On the other hand, chronic disease patients who go back to the office within a few days may do just as well to wait for an overnight test when the physician can meet with that patient in several days and discuss the outcome of the intervention.

Now, why is this all important and relevant for blood cell counters and differential counters?

Technology today allows the development of analyzers that have truly sophisticated software and instruments can be developed to not avoid the clogs and clots and things that happened before, but recognize those and to make them simple and accurate enough. HemoCue, our point-of-care company, has developed a very simple white blood cell analyzer

that was actually designed specifically with the CLIA waiver guidelines in place trying to determine whether we could make an instrument that would meet the CLIA waiver guidelines and provide choice to physicians. It's a one-parameter analyzer, much like the hemoglobin analyzers in use today as CLIA-waived devices. There are 30 error codes built into the software that flag things that can wrong so that a medical technologist is not required to run the system. It produces a white blood cell count result, much as a physician would do using a microscope, only it does it more accurately. There's no flow in the samples, no opportunities for clogs, et cetera.

So what's exciting about this product and what I wish our pediatrician evaluator could come to speak to you about is very similar to what Dr. Snyder spoke to you about. Like many pediatricians, they're under pressure when a patient presents with a fever, fluid in the ears and are not sure how to differentiate, whether they can differentiate between a viral and bacterial infection.

This particular physician found, even in the absence of a granulocyte count, with an elevated white blood cell count of both 15,000, fever above 101, and presence of fluid in the ears, she

prescribes antibiotics. When those three parameters are not met, she did not prescribe antibiotics and she reduced her antibiotic utilization when patients presented with those symptoms from 46 percent of patients to 6 percent of patients, a very significant drop in antibiotic utilization.

Now, obviously the concern is that a false positive could exist or a false negative could exist rather and a patient who needed antibiotics didn't get them. So she tracked the patients and she found, in fact, that she was appropriately providing the antibiotics to those patients that needed them. So she's very enthusiastic, and I wish she could be here with you to share her experience.

Now, why is that important? Because very few pediatricians have moderately complex laboratories today. Most of you who know, who follow the economics, know that pediatricians have very low-income levels today. They can't afford the additional costs of operating a moderately complex laboratory.

So is it possible for a pediatrician to operate a CLIA-waived system? We believe it is with the right technology available to the pediatrician to dramatically reduce the use of antibiotics.

So again, the point is offering choice. In the case of a child that presents with those conditions, a pediatrician does not have the opportunity to wait until the next day for CDC results to be available. They often don't want to send the patient to the hospital to get a stat result, and even if they do, it can take hours to get that result back. If they're in a remote location, that opportunity may not exist. What happens today, they get antibiotics.

And many of you know that preschools today require antibiotic utilization to get a child back into preschool. So the parent puts pressure on the pediatrician, although when you talk to the parents, some of the parents will say, no, the pediatrician provides the antibiotics even though we don't necessarily want them because they're not quite sure what to do. So they take the easiest route out which is to protect the children against the possibility of bacterial infection.

So what Dr. Casey found was with this objective evidence in hand, she could make a logical competent clinical decision and have evidence to show to the patient or the parent of the patient that satisfied their needs as well.

In conclusion, we encourage the Panel to support the notion of selecting the appropriate products for waiver that provide the benefit to aid the diagnosis, treatment, and monitoring of disease, and we encourage the industry to develop products that are not merely smaller versions of existing instruments but instead are designed to meet the stringent requirements for a CLIA-waived lab where the physician has the expectation that lab-based quality can exist at the point of care, and we believe that is possible today with current technology.

Thank you for your consideration. We look forward to working with the Agency as you move forward. Thank you very much.

DR. ADCOCK: Is there anyone else in the audience who would like to address the Panel now? Please raise your hand and come forward to the microphone.

(No response.)

DR. ADCOCK: Does anyone on the Panel have any questions for any of the speakers? None at this time? Dr. Bull.

DR. BULL: I have a question for the first of the speakers who mentioned that two -- I guess

maybe it's a question that he raised, but it may not be directed towards him, and that is if a waived test for CBC were to be granted, that this would decrease the instance of quality control, quality assurance overall for presently running tests, and I'm not sure that I understand the connection there. Can somebody from the FDA help me or could the speaker explain why this would occur?

DR. ADCOCK: Mr. Osmond, you may approach the podium.

MR. OSMOND: Yes, I can. The FDA just approved some chemistry equipment that is waived complete metabolic profile, and the manufacturer, out of the goodness of his heart, told the customers to drop proficiency testing and to opt out of being inspected by any outside agency, sent a letter out. So what is going to happen is the ones who now are not waived, who have hematology equipment, are going to decide that they don't need proficiency testing, they don't need quality people, and they don't need these outside agencies. Maybe Mrs. Yost can answer that better than I can.

DR. GUTMAN: Yeah, I actually think, my guess of why you would have suggested a degradation of frequency would be that it is true that waived

tests, in fact, do in general have different frequency, not as stringent frequency of QC. So I thought that you were going to say that there would be a shift to waived tests in order to eliminate QC. I don't think waiver of this test will have any impact at all on the requirements of moderate or high complexity labs. So the question would be whether there would be some incentive for moderate labs to become waived, not inherent a change in requirements for moderate or waived.

DR. BULL: I'm still confused. If a moderate complexity laboratory is doing a CBC and the CBC with I presume other equipment can be done in a waived laboratory, is it possible for the moderate complexity laboratory to just stop doing QC on the grounds that it's a waived test now? I don't know who to address the question to. It's presumably somebody --

DR. GUTMAN: Judy will have to correct me if I'm wrong, but my understanding is that the moderate and high complexity rules trump the waiver.

DR. BULL: So in order to avoid quality assurance testing, the laboratory would have to change its equipment and use the waived equipment and at that point, it would need to -- if that was the

desire of the laboratory director, they'd have to get rid of their moderate complexity testing and go to waived testing for that particular test?

DR. GUTMAN: That would my interpretation, yes.

DR. BULL: I see a lot of heads nodding. So I guess that's the answer.

DR. AZIZ: I think that's correct.

DR. WANG: That brought up a question. I would like to know if the waived is test-specific or equipment-specific, that is, I'm sure a lot of equipment can do CBC. So is the application for a waiver of CBC test or a particular equipment that does CBC?

DR. GUTMAN: No, it's specific equipment that meets -- you're going to have a discussion from FDA speakers that will talk about the specific requirements for waiver. It would be product by product. So you would have the same product. It would be possible to have a CBC that might be high complexity, that might be moderate complexity, or that might be waived depending on its operational features.

DR. ADCOCK: Any additional questions from the Panel at this time?

(No response.)

DR. ADCOCK: At this time the FDA will begin their presentation. Ms. Josephine Bautista will give the FDA presentation overview.

MS. BAUTISTA: Good morning. My name is Josephine Bautista. I'm the Associate Director for Hematology Devices in the Office of In Vitro Diagnostic Devices.

I'm going to give an overview of the purpose that we're here for, just a basic purpose overview, as well as some of the importance and relevance of this meeting, and also will be introducing the speakers.

The purpose of this meeting is to discuss if automated differential or automated hematology devices, CBC, with or without differential cell counters can be waived. And I would like to add here that this is an issues panel, and we're not discussing any particular device. We're discussing CBCs, parts of CBCs, differentials, three part and five part differentials. So we brought this to the Panel so we can discuss all parameters at this time so we can get a feel of what we need to do as far as a waiver situation.

If we decide to waive this device, then we

need to set up parameters as to how we're going to go about the performance of this device. At this point, we do not have a specific performance set for these kinds of devices. We have waiver of criteria and so forth, but these devices have some issues as far as meeting the waiver requirements, and these are some issues we would be looking at today.

Why is this important? Well, these are important to us, first of all, because this is a first of a kind device. We do not currently have a CBC with or without differential cleared or approved for waived status. And the reason that we don't have this is because currently most CBC devices are professionally used devices, and the reason is that the level of experiences that are required to interpret and analyze these types of devices, and at this point, we haven't had a CBC or differential submission that has been able to meet these requirements.

We also look at the risk and benefit associated with these types of devices. The benefits, of course, are to the patient and the physician because they're able to get these results in a more expeditious manner, they can have them on site and so forth, and we understand that, but there

are risks involved with these devices which means that we have a risk of erroneous results. There's always that possibility that these results that are on these devices cannot be as accurate as they would be in a laboratory setting.

There are also many questions and many issues that we have that we just haven't answered, and we need to get some explanation and input into how we're going to go about waiving these types of devices. And the problem with this is that we have issues such as how can errors be mitigated in the waived setting. We also like to figure out how are questionable results validated, and when I say questionable results is that, you know, in the laboratory setting you have flags, you have histograms, you have indices and other parameters to assist you in making the decision on the accuracy of those results. In the waived setting, you won't have that.

So we struggle with this question because we don't know how these kind of questions are going to be answered and how can you validate these assays. We wonder what acceptable level of risk is acceptable for these types of devices. I know that there are going to be some risk level there, but in some cases,

you know, we haven't decided how much risk we can allow for these types of devices.

And you also need to understand and try to figure does the untrained user have the ability to interpret and analyze these types of results, and those are important questions that we just don't have at this point, and we need to have. And we ask for your input on these questions.

Since this is the first time that we brought before our Advisory Council Panel the issue of CLIA waiver, we've divided our presentation into two parts. The first part we're going to give you a general overview of the CLIA program, how the CLIA process is as far as waiver of device, and some of the statistical requirements such as accuracy that are required for the device. And in the second part we will be more specific. We'll get more into what we see as far as the CBC and differential and some of the statistical requirement for those type of devices as well.

And with that, I will introduce our speakers. We have Mrs. Carol Benson, who is our first speaker, and she will be giving you an overview of the CLIA program as well as our new CLIA guidance document that we just approved in January. So she'll

give you information on that.

She will be followed by Dr. Kondratovich who would also give you information on to how you demonstrate accuracy. Accuracy is a very important part of the waiver process. So she will give you information on that.

She will be followed by Dr. Robert Becker, who will give you clinical and laboratory input on the CBC devices and information on how they're done in the laboratory setting and so forth.

And our last speaker will be Dr. Russek-Cohen, Estelle Russek-Cohen, who will give you some statistical analysis on some of the information as far as these specific parameters involved with the CBC device.

And with that, our first speaker will be Ms. Benson.

MS. BENSON: Thank you, Josie. My name is Carol Benson. I'm the Associate Director in the Division of Chemistry and Toxicology Devices.

The focus of our meeting today is about CLIA waiver for hematology devices, but I will be talking about CLIA waiver in general terms that will serve as an introduction to CLIA waiver. I will be discussing the impact of CLIA waiver and the concepts

of how a test system qualifies for CLIA-waived categorization.

What are CLIA-waived devices? If we go back to the regulation, we find that they are simple laboratory examinations and procedures that have been approved by the FDA for home use or are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that (A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or (B) pose no unreasonable risk of harm to the patient if performed incorrectly.

I'd like to point out that there's an "or" between (A) and (B). It's (A) or (B), not an and.

What is the impact of CLIA-waived test systems? Certainly, it is driving technology. There are many more simple devices that are on the market today. From the manufacturer's point of view, it broadens the market. The tests that are performing moderate and high complexity make up about 17 percent of all the CLIA labs. Those doing waived tests make up about 60 percent of all the CLIA labs.

There's truly a benefit for patients. We know that the tests and the results of those tests

could be present at the time of their visit with their physician. It could help with the personnel shortage of trained laboratory workers because waived test systems have no requirements for trained laboratory workers. There's also no requirements for proficiency testing. You simply get a class certificate from the Centers for Medicare and Medicaid Services, CMS, and "follow manufacture's instructions."

If we look at how tests are categorized, we see they're categorized into three areas, waived, moderate and high. If we look at the first bar, that's the number that have been waived over the past five fiscal years. We notice that they are increasing. At the same time, those tests that are high, which is the third bar, they have decreased in the past fiscal year. The middle bar is the number that are moderate complexity. That makes up the majority of the test systems.

How do test systems qualify for CLIA waiver? There are three routes to CLIA waiver.

By regulation, we have nine generic tests that are automatically waived. The fecal occult blood, the urine pregnancy, the urine dipsticks, the over-the-counter glucose meters, a spun hematocrit,

an ovulation test, a single analyte instrument for hemoglobin and a hemoglobin by copper sulfate, and the erythrocyte sedimentation rate.

Another way is by FDA clearance and approval for home use. That's another way to get waiver.

And the third way is by meeting the statutory criteria with valid scientific data which is the focus of our meeting today.

If we look to the CLIA waiver history, we find that over a decade ago, CDC with CMS proposed a rule that outlined CLIA waiver criteria. In 1997, the FDA Modernization Act clarified that all tests that are cleared for home use are automatically waived. In 2005, FDA drafted a CLIA waiver guidance, received comments from this guidance, and published a final guidance in January of this year. The guidance is in your packet for information. We are not going to be asking you to provide comments on that guidance.

What is in the guidance? Where did the comments come from?

It arose from information that we received from our Advisory Committee from the CLIA, the CLIAC people, from our sister agencies, from CDC and CMS,

from medical device industry, from trade associations like AdvaMed, professional associations like the American Association for Clinical Chemistry, and laboratorians in the field.

It's based upon FDA's interpretation of the law that I read to you in the first few slides of my talk.

I'd like to point out that there is a difference between guidance and the law. Guidance is not binding. The law is binding. The guidance merely recommends how to meet the law.

The principles of the guidance include the idea of using intended operators, those that would be in a waived setting to perform testing on a proposed device under stress while they're multitasking, testing real samples over time, and our minimum suggestion is for two weeks.

Then the results of the waived test will be compared to another method which we are going to be calling a comparative method of which we base the accuracy of the waived method.

There would be traceability requirements for the comparative method. That means there would be a degree of trueness to the comparative method.

We would ask for a risk analysis to base

flex studies. A risk analysis would be an identification of all the things that could go wrong. Flex studies would be studies done to stress the system to determine if the system will fail and where if it doesn't fail and do the failure alert and fail-safe mechanisms prevent results from occurring?

And we believe that we are asking for clinically based performance standards on which to base accuracy. These we've identified as allowable total error, ATE, and limits of erroneous results. The allowable total error will be the amount of error that can occur between the waiver method and the comparative method, and the limits of erroneous results are areas in which we would expect that there would be no results observed.

For qualitative tests, we have requirements for controlled cut-off studies, and for all devices, we want to ensure that the device is controlled at its critical cut points. We realize that in this guidance that one size may not fit all. There may be other approaches to CLIA waiver, and we do encourage protocol reviews with FDA through our pre-IDE process.

CLIA-waived test systems are used at point-of-care sites. We believe that a point-of-care

device is one that is used near the patient by health care professionals, for example, in the doctor's office, in a nursing home, in an emergency room or in a clinic.

There are similarities and differences, though, between CLIA-waived devices and point-of-care devices. We know that CLIA-waived devices are usually performed at point-of-care sites, and both CLIA-waived and point-of-care device have studies that demonstrate their performance at a point of care, but there are differences.

Many of the point-of-care devices are categorized as moderate complexity, and this simply may be because, one, they may not be simple and, two, they may not have performed CLIA waiver studies to demonstrate that they actually meet the CLIA waiver criteria.

How does a test system meet the CLIA waiver criteria? Two basic questions needed to be answered. Is the test system simple? Does the test system have an insignificant risk of an erroneous result?

In the guidance, we've listed some points which we think would demonstrate simple. That would be a fully automated instrument or like a unitized test system, one that would use fingerstick blood

unprocessed samples like fingerstick blood or venous whole blood or urine, not serum or plasma. That there would be no technique-dependent specimen or reagent manipulation that would occur during the testing, and that there would be no operator intervention during the analysis, and that there be no technical or specialized training with regard to troubleshooting or complex error codes to interpret. There would be easy-to-read results. The results would be positive, negative. There would be a value, and there would be clear labeling.

What type of labeling are we recommending? We're recommending quick reference instructions that would be written at the seventh grade reading level, with pictures and diagrams of how to perform the test. There would be the package insert with procedure steps that would be written at a seventh grade reading level, and we believe it should include quality control recommendations for the use of external ready to use type quality control materials, and there would be a recommendation for the frequency of testing. And we are encouraging education material to be provided so that this would help when there's a turnover, the waived people, that educational materials might help them understand the

test system better.

How do you determine an insignificant risk of erroneous results? You perform a risk analysis and identify all the potential sources of error and then how would you mitigate those sources.

The risk analysis might include errors such as operator, which would be considered human-factor errors. There could be specimen handling and integrity issues. So the specimen could be clotted or there could be interfering substances. There could be a reagent integrity problem. The storage might not be properly stored or the reagents could be outdated. Maybe there are hardware, software, and electronics problems such as power failures or software bugs, or there could be like physical trauma to the instrument if it's plugged or unplugged or moved. And the system would need stability. The calibration especially would need to be stable. And are there factors that affect the environment such as heat and humidity or are there electrical or electromagnetic interferences.

After the risk analysis is done, then we need to test the fail-safe and failure alert mechanisms that would be validated through our flex studies, which are our stress studies.

What are some fail-safe and failure alert mechanisms? There could be lockout features such as there would be no result, say, if expired reagents or if the internal electronic checks fail or if the quality control fails. There could be a physical feature that would be a fail safe that would ensure that the strip or the cartridge are placed in the instrument correctly each time.

Failure alert mechanisms are more like monitors of the environment for like temperature or humidity, and external quality control materials and internal procedure controls.

The flex studies that I talked about are stress studies that would be based upon the risk analysis. Say the potential source of error is what happens when too many or too few drops are added to the test cartridge. The procedure says to add three drops. So you could set up a study to stress the system by adding one drop or adding two drops and adding three drops and four drops and five drops and six drops and find out where the incorrect result occurs. The device fails at one and five and six drops.

Then we would say, well, do the fail-safe or failure alert mechanisms mitigate this risk by

alerting the operator when too few drops, like less than two, or too many drops, greater than four, are added. Sometimes the internal procedure control can do this.

Another potential source of error would be like use of expired reagents or reuse of cassette or reagent pack. You could do studies that would try to use expired reagents or to reuse a cassette. Again, you would see if this risk is mitigated by the fail-safe and failure alert mechanisms that they alerted the operator that something was wrong or it was a lockout feature.

Another potential source to bear is improper storage, and again, you go through the same process. Stress the system, find out where it fails, find out if your fail-safe and failure alert mechanisms identify these conditions.

After we determine that it's simple and done the risk analysis, then we want to go to valid scientific studies for accuracy. We want to use the labeling and the education materials only to test the system.

Demonstrating insignificant risk of an erroneous result and accuracy. We say the term accurate refers to those tests that are comparable to

traceable methods. They have a degree of trueness because many test systems do not have reference methods or reference materials. We expect that they would be perspective, clinical studies of the device that would be proposed for waiver, and we would ask that it be tested in three clinical testing sites and use at least nine different operators, and that they would test 360 samples over a time period for a minimum of two weeks we're recommending, and at the end of the study, they would do a user questionnaire to find out about the ease of the use and did the user understand the labeling.

The demonstrating accuracy is based upon the paired sample design. The paired sample design has one sample that's used for the waiver method and one used for the comparative method. And then you would compare the results. The comparative method would be performed in the laboratory setting by the laboratory professionals.

The criteria for accuracy. For quantitative tests, we would say that you need to establish what is the allowable total error, what is the amount of error that can be acceptable between the waiver method and the comparative method and what are the limits of erroneous result zones for the

analyte in question. Establish those before the study beings.

For qualitative tests, we're going to be looking at the percent agreement between the waiver method and the comparative method.

We realize that some analytes have existing performance limits for professional use found in the CLIA regulations. For example, leukocytes have limits of plus or minus 15 percent. However, many analytes do not have performance limits for professional use in CLIA. So, therefore, we feel that they need to meet the clinical needs for the analyte.

We're going to hear more about how accuracy is evaluated from our statistician, Dr. Marina Kondratovich. She will talk about how to establish and evaluate the allowable total error, that is, the differences between the waiver method and the comparative method, and she will talk about how to establish and evaluate the limits for erroneous results, and which we would expect there would be no results in the observations during the study.

Thank you.

DR. KONDRATOVICH: Good morning. My name is Marina Kondratovich. I am statistician from

Division of Biostatistics, and in my presentation, I will speak about accuracy.

I will touch some basic points related to accuracy as traceability, total error, allowable total error zone, and limits of erroneous results zone.

You probably see already this definition, what does mean test for CLIA waiver, and I would like to emphasize for my presentation that it employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible.

Risk analysis, flex studies, fail-safe and failure alert mechanisms is already discussed in presentation by Dr. Carol Benson, and in my presentation, I will consider only accuracy.

First, let's discuss what is the meaning of accurate test? In FDA CLIA waiver guidance, there is this interpretation. The term accurate tests refers to those tests that are comparable to traceable methods, or well-documented methods.

So here there are two important terms, comparable and traceable. So let us discuss what is mean traceable? What is mean comparable? And I will present basic, general information for general

concept related to CLIA waiver, and all this concept is only applicable to the quantitative tests.

Please note that the tests which we consider today during our Panel meeting are quantitative tests, not qualitative.

Traceability. The formal definition of traceability is following: the traceable method is a method in which results of measurement can be related to stated references, usually national or international standards, through an unbroken chain of comparison. And in plain language it means that traceability requires an established calibration hierarchy.

And this is the basic idea of traceability. Imagine that we have three calibrators, calibrator 0, calibrator with concentration 1, with concentration 2, and all these calibrators are some kind of related to the reference method or reference material.

What is mean related? Like, for example, these two samples were measured by reference method and you know true value of this sample. Then we need to construct calibration curve using all these three points.

What is mean calibration curve? Calibration curve is relationship between signal of

the system and all these two concentration. So it's easy to understand that if calibration process is done appropriately, we can expect that traceable method has almost no systematic bias. So traceable method has set kind of measurement values that have almost the same degree of trueness as reference method or reference materials. So systematic bias is relatively small.

If traceable method has a high imprecision, large random error, then a few replicates should be performed and an average of these replicates should be considered.

So we can make some kind of basic conclusions that if we consider average of few measurements by traceable method, then it will be approximately true value for the sample.

We discussed what is mean traceable method, but remember accurate measure is the method that comparable to the traceable method. What is mean comparable?

In order to use this concept, we can see that waiver method is comparable if the deviation of the waiver method results from the true value is acceptable. Deviation is difference between waiver method result minus true value. And deviation is

based on the concept of total error. I will discuss right now an acceptable -- concept of allowable total errors zone and limit of erroneous results zone.

This is the basic idea of total error. Consider that we have Patient A and we have sample from this patient. We have Patient B and we have sample from Patient B. And both of these patients have the same true concentration X, and we have some method, and we're applying this method to the sample from Patient A and to sample from Patient B. So same sample is tested over and over again under different conditions. And graph -- that for Patient A there is systematic bias. So this is the mean value, and the bell shape show me where is more frequently the result of the Patient A. So this is the random error. This is the green line. Bell shaped curve showing me that most frequently results around mean and less frequently results are here.

For the Patient B, we have mean value is here, and random error is probably maybe the same. So this is my random error for Patient B, but I would like to emphasize that because the amount of substances other than the analyte of interest vary from patient to patient, the systematic bias from Patient A can be different than for Patient B.

So we have this component, random matrix-related interferences, and this red component is related to particular method, and this blue component which is random matrix-related interferences related to the fact that we have really a different patient, Patient A, Patient B. Even if the patients have the same two concentration X, in our review of waiver study, we would like to have real patient samples because archived or back specimens may not be used in these type of devices.

So for individual measurement for a given sample K, deviation of waiver method results minus true value consists of three basic components, systematic bias which are related to what kind of method you use, random interferences and random error which are related to imprecision.

In order to evaluate a random matrix-related interference component, we need to have samples from different patients and in CLIA waiver study, recommend to have at least 360 different samples.

Third component, random error imprecision is really related to what kind of condition you have, and we really need to have different conditions like different site, different days, different operators,

in order to evaluate random error. In the CLIA waiver study, it is recommended to have at least three independent sites, I mean sites in which will be used CLIA waiver test, at least nine independent operators and at least two weeks of duration of the CLIA waiver study.

The clinical studies for evaluating accuracy should compare results obtained with the device proposed for CLIA waiver to results obtained by comparative method.

The basic statistic paired study design means that from the patient you obtain sample, you can divide the sample in two parts, or if it's impossible, you can have maybe a second sample like in this example. For example, for waiver method, you are taking one sample like fingerstick blood and applying waiver method. You can take second sample like venous whole blood and apply to comparative method. Waiver method should be performed by untrained user in CLIA waiver setting, and comparative method should be performed by professional users in laboratory settings because really we're evaluating deviation of waiver method results from the true value. So we really would like to have true value, the best what we can have, the

closest to the truth as possible.

For this, we need to have selection of comparative method inside kind of hierarchy. The reference method, if available, then in order to obtain the true value one needs to use reference method. If reference method is not available, one needs to use traceable method. Let me remind you that traceable method has very small systematic bias or some kind of well-documented method.

Waiver method results minus true value can be presented on the plane with axis X where on axis X we have true value and on axis Y we have waiver method results. So for any patient, we have this point on the plane where X is true value and waiver method is Y. All points on diagonal present -- kind of waiver method results that really there are no -- error because this point exactly on the diagonal. Waiver method is same like true value. This interval is really deviation of waiver method results from the true value.

So what kind of deviation are acceptable. For this, we need to establish allowable total error zone. Values of waiver method that fall within allowable total error zone are values that can be tolerated without invalidating the medical usefulness

of waiver method results. Allowable total error zone is the zone around the diagonal, meaning it contains very small errors or including no errors which diagonal. It is anticipated that no less than 95 percent of sample results will fall within allowable total error zone.

But even if we have 95 percent in this allowable total error zone, 5 percent of the sample can be outside of the allowable total error zone. So we really need to establish that kind of zone which are really prohibited for waiver method test.

So this is limits of erroneous results, this dark gray zone. Values of waiver method that falls within limits of erroneous results zones are values that pose a risk to a patient's safety. Potential harm can occur to the patients if these waiver method results are utilized in medical decision-making. Limits of erroneous zones are outer zones. For example, this point definitely belong to the limits of erroneous results zone because this zone presents that kind of waiver method results, which are really relatively low when the true value are high, and here is opposite situation. This is the point definitely belong to the limits of erroneous results because in this point true value is

relatively low, but the waiver method has very high values.

It is anticipated that limits of erroneous results zone contains no data if you have in your study 360 samples or little data if study has larger sample size.

So we will ask you input for allowable total error zone when we're expecting 95 percent of the samples in the study, and also for the limits of erroneous results zone, we expecting 0 percent of samples in study of 360 samples. I would like to emphasize that both zone, allowable total error zone and limits of erroneous results zone should be established before the CLIA waiver study.

Also, I would like to emphasize that, of course, from the clinical point of view, is good to have allowable total error zone, for example, the smallest as possible, almost like close to that diagonal, but in this situation, almost impossible to pass this criteria because we know that all tests have some kind of variability. So when you establish an allowable total error zone, it should be some kind of balance between what is realistic expectation for the test performance and what is the clinically acceptable because if one establish very broad

allowable total error zone then, of course, it's easy to pass, but maybe it's not clinically acceptable. And opposite, of course, clinically it's very good to have small allowable total error zone, but it's impossible to pass because every test has variability.

How to set the allowable total error zone. Of course, it depends on intended use, and in CLIA FDA waiver guidance, there are some hierarchy, what kind of approaches you need to consider when you establish an allowable total error zone.

First, analyze listed in CLIA 88 regulation, you need to use performance goal for professionals if this analyte is listed in this CLIA 88 regulation. For example, CLIA 88 regulation has acceptable limit for white blood counts and the acceptable limit of plus/minus 15 percent and it's anticipated that this limit will be used.

Also I would like to emphasize that can be different rules when defining allowable total error zone for different ranges of comparative method. Like for example, in this example on this figure, for high values of comparative measure, usually we use boundary for allowable total error zone like percent, like proportional boundaries because if you continue

to have percent, even for the low values, finally you obtain that, for example, for 0 concentration it should be deviation 0. Of course, it's impossible to have because we know that even for a sample with no analyte, there is noise background. So usually for their values of comparative method which are relatively low, it's possible only to pass criteria with some kind of like constant.

Also, very oftentimes the clinical point of view, it's also clinically acceptable because there are no meaning to calculate percent for example for the unit 1. If your true value 1, and your waiver method you value 2, of course, proportional error is 100 percent, but we limit to calculate absolute values. Absolute values is only 1.

If analytes is not listed in the CLIA regulations, other criteria may be acceptable.

First, what kind of approaches we can use? First published professional recommendations from national and international expert bodies. If it's not available, one can start to evaluate the effect of analytical performance on clinical outcomes. Also we can use approach based on components of biological variation and let me give a few more words about this approach based on component of biological variation.

If the patient is undergoing monitoring of analyte, and here what is mean monitoring, I mean that we're measuring the analyte of the patient at different time points, the variation from measurement to measurement, this is variation from measurement to measurement, consists of two parts. One part is variation which are related to biological components. This is the variation within subject. And the other is component which are related to analytical, how precise you measure the same sample, and here even we have the same patient, the sample can be little different during the time.

So imagine that we have standard deviation for analytical variability which is only fraction for biological. Then, of course, standard deviation of measurement will be influenced most of the time biological variation. So the larger within-subject biological variation, the larger analytical errors can be tolerated because a standard deviation can be only part, faction, of the biological variation, the larger biological variation, the larger can be analytical error.

So Carol Benson already described basic study design for CLIA waiver study and more details you will hear in the presentation of Dr. Russek-

Cohen.

Here we have these examples, 360 patients in the CLIA waiver study and this is some kind of visualization data of the CLIA waiver study. This is our allowable total error zone, and we need to calculate what is the percent of the subjects inside this green zone, allow total error zone. We expect that at least 95 percent of subject in this zone. We also need to calculate percent of waiver method results for low, medium and high ranges and we're expecting that this percent close to 95 percent.

When we're calculating percentage of waiver method observation over entire range and we have 360 samples, 95 percent of the samples inside the allowable total error zone, low bound of 95 percent confidence interval is 92.8. It means from a statistical point of view, that we are sure that not less than 92 percent of patients from the intended use populations have waiver method result in allowable total error zone, which are clinically acceptable.

Also we need to calculate what is the percent of subjects in limits for erroneous results zone, and we expecting that in this zone, it will be no or little data. For 360 samples, if we observe

that there are no data in this zone, then upper bound of 95 percent confidence interval is 0.8 percent. It means that we are sure that not more than 1 percent of patients from the intended use populations have waiver method results in the limits of erroneous results which are harm for the patient.

So we need your input, you will see one of the questions, on allowable total error zone and limits of erroneous zones for hematology devices which you consider during this Panel meeting, and more statistical details related to these devices will be presented by Dr. Russek-Cohen. Thank you very much.

DR. ADCOCK: Thank you. I think perhaps the Panel might choose to ask questions of the speakers at this time. So perhaps we can take questions from the Panel.

DR. KULESZA: I have a question to Dr. Benson actually, not to Marina. It's just for my understanding. When you were talking about CLIA waiver guidance, you were talking about controlled cut-off studies. Can you elaborate? Scientific issues for qualitative tests are addressed in controlled cut-off studies and ensure that the device is controlled at the critical cut points. What does

that mean?

MS. BENSON: Okay. For example, it could be a quantitative test where the cut off is 1.0, that's very low. So we want to be sure that that 1.0 is well characterized, that that has accuracy and that that test is controlled there, that the 1.0 is going to be 1.0 from lot to lot, that each time the person does the testing.

DR. KULESZA: So I understand it to mean also that you will include particular provisions of testing of actual analytes within the group of a study that falls below that range and above that range.

MS. BENSON: Right.

DR. KOST: Both speakers mentioned 360 as the number for evaluation. What is the source of that number? What is the power of it in discerning differences, et cetera?

DR. KONDRATOVICH: As I mentioned, basic deviation are based on the concept of total error and particular range, in order to evaluate total error, it is recommended to have at least 120 samples. From statistical point of view, it's related that we need to evaluate some kind of percentiles with confidence. So it is recommended to

have a least 120 samples in order to establish total error for particular age, but usually we have three ranges, like for example, low values of comparative method, medium values and high values. So you really need to have approximately 120 for any particular range in order to evaluate total error.

DR. KOST: What is the basis of the 120?

DR. KONDRATOVICH: 120 is based on the non-parametric estimation of the percentile because we really would like, for example, we can have 2.5 percent outside of the zone and 2.5 percent outside of this zone. So we really need to evaluate percentile and minimum requirement for evaluation percentile at least to have 40 samples, but in order to have good confidence interval for this percentile, one need to have at least 120.

DR. KOST: If you approach things non-parametrically, why do many of your examples show what appear to be normally distributed error?

DR. KONDRATOVICH: Yes, I absolutely agree with you because for simplicity in my presentation, when I consider the concept of total error, I consider bell shaped curve because it's like some kind of fashion in studies. I agree with you sometimes. It can be not normal distribution, but

you can make some appropriate transformation and you can obtain normal distribution. This is for simplicity, that I consider random errors normal.

DR. KOST: Well, in some of your other illustrations, you use standard deviation as well. Why don't you display those things non-parametrically? Some of these slides like your setting allowable total error zone --

DR. KONDRATOVICH: Uh-huh.

DR. KOST: -- you illustrate things as standard deviation, et cetera. Are you making a tacit assumption of a normal distribution?

DR. KONDRATOVICH: You speak about --

DR. KOST: Slide 23.

DR. KONDRATOVICH: Uh-huh. This is a basic concept, yes, when you're trying to calculate what kind to, you can use some more complicated approaches in order to understand how your analytical measure related to the variability of monitoring if you have biological variation. And again, this is for simplicity. I consider that this is normal model only in order to give you basic idea of how analytical error can affect measurement error if you have biological variation. I absolutely agree with you. It can be non-parametrical also. And there are

very good books. So I suggest to you to see more details if you're interested in this document for non-parametric.

DR. KOST: In more than one instance, you mentioned comparison to laboratory setting --

DR. KONDRATOVICH: Uh-huh.

DR. KOST: -- as the reference method but actually with point-of-care testing, there may be reasons that there are pre-analytical changes over time and therefore transit or use of a laboratory per se may be inappropriate. Another way of viewing it might move the laboratory to the point-of-care setting or move the point-of-care instrument to the laboratory so as to eliminate those pre-analytical temporal differences.

DR. KONDRATOVICH: Yes, I absolutely agree with you.

DR. KOST: Could you clarify please?

DR. KONDRATOVICH: Yes. So it's really because I'm speaking about so general stuff, we need to decide case by case what kind of situation, and I absolutely agree that sometimes it's so difficult to control for example stability of the sample, that when you move the sample to laboratory study to have some pre-analytical issues important, then we need to

think about how to design the study in order to evaluate this test in unbiased way. So this is the reasons that we encourage the sponsor to come to us to discuss the ideas because it's really difficult to describe study design which fit for all situations with a lot of details.

DR. KOST: Uh-huh. And slide 17 and subsequent slides, your plot is an X-Y plot.

DR. KONDRATOVICH: Yes.

DR. KOST: But clinicians often favor a different plot based on Bland Altman type display, differences against average and --

DR. KONDRATOVICH: Yes.

DR. KOST: -- one thing that's handy is to modify the Bland Altman plot somewhat and show differences against a reference method rather than an average on the X axis. Have you considered that or is there a particular reason not to use the Bland Altman? It's considered the prerequisite in clinical journals now, many to use this portrayal because it's easier to interpret than this X-Y plot.

DR. KONDRATOVICH: There are some -- in reality, here the value comparative method is different from waiver method because the comparative method is like reference methods which is the true

value. My point that when you consider Bland Altman plot and consider average X plus Y divided by 2, you really put the same weight on the X method and the Y method, but here comparative method is absolutely different way. So we really would like to have difference between waiver method and comparative method, not difference compared to the average of waiver method and comparative method.

DR. KOST: Well, that's what I'm saying. Modify the Bland Altman to --

DR. KONDRATOVICH: Yes --

DR. KOST: -- put just the reference method on the X axis.

DR. KONDRATOVICH: -- you're absolutely right. I agree with you, another way to present the same information that you can show comparative method and only these differences. This will be exactly your plot of differences. So it's like this. Instead of showing entire this point, you can show only this interval. So formally, it's almost the same. You only need to rotate your graph. So I decided because of shortage of time not to show both type of presentation, but they absolutely present the same amount of information if you present X and Y or you present X versus Y minus X. But I agree,

definitely we're asking during our submission to present both because sometimes it easier to see better. You have more presentations the same day, maybe it can be easy to review. But my point, the amount of information in both graph are the same.

DR. KOST: The drawing of your prohibited zones in slide 18 and other materials I've seen is peculiar in that perhaps it's not evidence based, and sometimes in the lowest ranges of an analyte, we have some of the greatest clinical risks implying that the prohibited zone would come much closer than you've drawn it.

DR. KONDRATOVICH: Yes. Of course, you see --

DR. KOST: And I just wonder, I'm cautious in today's discussion that perhaps we need to be more evidence based about how we draw these zones. So you stated several times that it's necessary to have these zones prior to considering a device for approval --

DR. KONDRATOVICH: Yes, try to --

DR. KOST: -- but then on the other hand, we're in a paradox because we don't really have the evidence to draw those zones. Do you have any comment on that?

DR. KONDRATOVICH: First, about this particular example, you see that even I tried to draw this line by hand in order to show that it's really hypothetical --

DR. KOST: Yeah, I see it's by hand.

DR. KONDRATOVICH: It's not like I'm describing particular device. I'm really trying to present hypothetical situation, and one of your questions will be more precisely where it should be the zone, and you are right. Sometimes it can be very close to the zone.

DR. GUTMAN: Let me interject because that speaks to the Panel, the fact that we as a workgroup are having difficulty arbitrarily mining the literature or mining practice standards to create, both of these parameters speaks to one of the reasons we're having this Panel, you know, this Panel is our surrogate for an expert voice. One suggestion could be there isn't enough evidence to make these decisions. One suggestion could be based on our experience, here are the areas of minimal harm and here are the areas of practical total allowable error. That actually speaks to about half of the reason we're having the Panel is to ground exactly that question in your angst or your wisdom.

DR. KOST: Uh-huh. And in the course of the day, I'll try to suggest that an alternate statistical method for looking at point-of-care testing because I think historically as the field has evolved and now we hear from the audience members, of course, that it's evolving very quickly, perhaps too quickly, it may be time to take a second look at how we assess accuracy and see if we can make our assessment of accuracy more clinically relevant, and there are technical statistical details such as getting away from parametric statistics.

The plot you drew which, of course, has obviously meritous simplicity, it's nonetheless somewhat of a suggestion toward the ALA glucose testing, Clark grid, and others, and we find, you know, in data that we've published that the Clark grid and some of these are irrelevant because the zoning is very empirical (a), and (b) now some of the devices are so accurate, they don't hit those outer zones. The data just isn't there at all. Thank you for answering the questions.

DR. NORBACK: I think, Ms. Benson, you described the flex study where the instrument would be challenged by adverse conditions.

MS. BENSON: Right.

DR. NORBACK: Could we consider extending that list to consider clinical situations and then challenging the instrument with samples that were hemolyzed and had plots and hyperlipidemia?

MS. BENSON: I think in the risk analysis, I sort of indicated that you should evaluate all the potential sources of error --

DR. NORBACK: Uh-huh.

MS. BENSON: -- and how they would they be mitigated, and the examples in the flex studies were just a couple of examples I gave you.

DR. NORBACK: Yes.

MS. BENSON: So that if you identified that bubbles would be a problem, or that clotted samples would be a problem, so then you would have to say how would I mitigate the risk of someone using a clotted sample or bubbles in the sample when it's introduced into the instrument.

DR. NORBACK: Then I have a follow-up question. So if a number of adverse conditions or challenging conditions are identified and we would expect the instrument to perhaps have a lockout feature so that very erroneous results were not reported, would these samples also be included in the clinical trial of your 360 samples?

MS. BENSON: Well, I think the idea of using the testing over time in a real setting is that during that testing, that some of those conditions might occur. We are suggesting like a month, but the minimum we want is two weeks so that you would have a real life situation because we know that there might be clotted samples, there might be bubbles in the samples when we put it into the instrument. And those should show up as errors against the comparative method.

DR. ADCOCK: What should happen if during that testing period, the lockout effect does not require use? Can there be some sort of a requisite that a certain number of samples do meet the lockout requirement?

MS. BENSON: I don't think we have an exact number of samples that should meet the lockout, but I think we should be convinced that whatever they propose for risk mitigation would be adequate for clinical use. And sometimes labeling, you know, might be a risk mitigation, but you can't rely on labeling for mitigating too many risks because we know people don't read labeling.

DR. KULESZA: But I mean the question is well put. I think you should be planning on

challenging the instrument with potential sources of whatever samples are inappropriate, whether they're half drawn or clotted or something.

MS. BENSON: Right.

DR. KULESZA: That should be a requirement.

MS. BENSON: Right. That should be part of the risk analysis and part of the flex studies.

DR. KULESZA: I have a question, is pre-IDE binding on a sponsor? Is pre-IDE discussion binding on the sponsor?

DR. GUTMAN: No.

DR. WANG: I have a question for Dr. Kondratovich. On your slide 21, if you draw the curve based on 95 percent confidence interval, we can understand that as the mean value gets bigger, so then the interval will get wider, but how come for the very low value you have actually widened interval, and also the boundary can be set as a constant.

DR. KONDRATOVICH: Yes.

DR. WANG: How did you pick the constant? Was there a statistical way to pick the constant or it just professional judgment?

DR. KONDRATOVICH: Professional judgment.

DR. WANG: Uh-huh.

DR. KONDRATOVICH: It's not statistical way to pick up exactly cut point where I need to start to use constant, but here my point, that imagine that you continue this line up to the zero. Then, of course, you obtain deviation from the two the smaller, the smaller, because absolute value is smaller and percent from this absolute value is also smaller. But then if it's 0, you almost require no error. So my point that really when you establish from clinical point of view, allowable total error zone, you don't need to set the same type of rule, like 15 percent for entire range. You can tell like here, 15 percent for the range which is more than 80 units and if less than 80 units, plus/minus 20 units for example, it's okay. You can even establish different percent for the different ranges. For example, for some range you can think that it should be different percent. So it can be different percent for this range but again it's based on the clinical judgment, not statistical, some kind of hypothesis or --

DR. KOST: Well, is your latter explanation or suggestion actually a reality because if you have these different percentages in the low, mid and high, then you have discontinuities in this concept. And

you can also, of course, get a discontinuity at the low end there if you're --

DR. KONDRATOVICH: You're absolutely right.

DR. KOST: -- you don't match the percent where they're supposed to connect. Is it a reality that you have used such discontinuous error description?

DR. KONDRATOVICH: Yes. Here it's exactly -- what we describe, it's exactly this point is continued there because 12 units is exactly 15 percent of the border. I feel that to use the zones which are not continuous is some kind of strange way. So here, ideally you see here, everything is very smooth. If you describe some kind of zone, that in some particular point, there are jumps, then probably it's very strange requirement from the clinical point of view but theoretically one can imagine that something, if this point, above this point you have one requirement to do is absolutely different but it's probably -- So usually all of these boundaries are smooth and continuous resulting in big jump. So when you consider this constant and percent, then you really need to do something from -- in order to have -- together.

DR. KOST: But my question is has such a

discontinuous model been used ever for any analyte to your knowledge?

DR. KONDRATOVICH: No, I don't have that kind of experience and I never saw that kind. In literature when there are discontinuity, there might be --

DR. KOST: Well, in the original NCCLS guideline for glucose, there was a discontinuity. It was removed in ISO15197 for glucose testing. Okay. So your experience is you haven't seen it in practice.

DR. KONDRATOVICH: No, we don't see it -- some kind of jumps but, of course, we don't have a lot of experience --

DR. KOST: Yeah.

DR. KONDRATOVICH: -- with this test. Maybe in future, we will have some new technologies, new analytes when we really need to care for discontinuity but not right now. I don't have this experience.

DR. KULESZA: I just want to add one follow-up point on Dr. Kost's. Regarding the values that are close to 0, I mean those can be in and how to make judgments about that zone, using empirical values or clinical consequences where we have an

opportunity to follow up on say patients with ITP or neutropenia, or other conditions that will fall into those border zones where you can't draw the noises sort of -- not allow -- well, error zones --

DR. KONDRATOVICH: Yes.

DR. KULESZA: -- and go down into the --

DR. KONDRATOVICH: Uh-huh.

DR. KULESZA: There will be times to discuss that further in terms of how FDA approaches the clinical relevant scenarios.

DR. KONDRATOVICH: Yes.

DR. KULESZA: Okay.

DR. KONDRATOVICH: Yes, definitely. And you will hear more details related to hematology in presentation by Dr. Russek-Cohen.

DR. KULESZA: Good.

MR. BRACCO: Marina, on slide 19, you state that 0 percent of the samples, I believe that's in the guidance --

DR. KONDRATOVICH: Uh-huh.

MR. BRACCO: -- should fall in the LER, and my question is the control method is not 100 percent perfect as well.

DR. KONDRATOVICH: Yes.

MS. BRACCO: So when the result falls in

the LER, it may, in fact, be because the control method is incorrect. How do you compensate for that when you say zero allowance in that particular --

DR. KONDRATOVICH: Yes, it's very good point. First, of course, it's good to have control method which is like reference method, and this is the reason why it's good to compare to reference or to traceable. If the comparative method has some kind of relatively large systematic bias, you're absolutely right. It's more difficult to pass. It's not good study design. You really need to have good comparative method. Another point, yes, comparative method can have random error. If you not eliminate this random error, then you can be in the zone because comparative measure has random error, not systematic. In this situation, you need to take few replicates and try to eliminate this random error in order that you really know what is your true value for this sample.

MR. BRACCO: Thank you.

DR. KOST: So are you saying when you review these data sets, that a duplicate or even three hits --

DR. KONDRATOVICH: Yes.

DR. KOST: -- on a single measurement or

maybe four or --

DR. KONDRATOVICH: You're absolutely right.

DR. KOST: -- are acceptable --

DR. KONDRATOVICH: Yes.

DR. KOST: -- as the reference.

DR. KONDRATOVICH: Yes, is acceptable and even recommended to have -- you can have one, but like you're telling, it's more difficult to pass. It's some kind of risk that you can be out of the zone because of the comparative measure started to be noisy. We recommend to have duplicate, but sometimes comparative method is relatively good.

DR. KOST: So are you saying that these studies should have all duplicate reference methods, measurements then?

DR. KONDRATOVICH: For during the PID, knowing characteristic of comparative measure and knowing how this waiver performs for example in the hands of professional, we can evaluate approximately what number of replicates should be done for comparative measure and then design study with this number of replicates.

DR. ADCOCK: I think at this time we'll take a 15-minute break. It's about 7 minutes after, I believe.

(Off the record at 10:07 a.m.)

(On the record.)

DR. ADCOCK: To the Panel members, if they could speak more closely into their microphones when they would like to ask a question or make a point.

At this time, the FDA will continue their presentation. I believe Dr. Becker is our next speaker.

DR. BECKER: Good morning. I'm Robert Becker, Chief Medical Officer for the Office of In Vitro Diagnostic Device Evaluation and Safety in the Center for Devices and Radiological Health.

You've already heard about general aspects of the waiver program for diagnostic devices under the CLIA regulation and guidance. I will speak for the next 20 minutes about laboratory and clinical issues attached to hemologic devices and especially to the potential use in a waived laboratory setting.

I'll provide a brief laboratory and clinical overview pertaining to peripheral blood counts. I will describe the hematology analytes that are the focus for discussion today along with some background on their measurement. I will touch on some practical challenges in counting blood cells. I will note some tradeoffs between depth of blood cell

analyses and the cost or accessibility of testing. These tradeoffs should be considered in the context of a wide range of uses for blood cell counting which can help in framing the benefit and risks from waiver. We seek input on how an appropriate balance of the risks and benefits can be met for waived blood cell counts.

FDA seeks input from the Panel concerning the suitability for waiver of devices used to obtain automated blood counts and differential cell counts. These are multiparameter tests that assess the formed elements of the peripheral blood. Automated cell counters have their own regulation and the complete blood count, or CBC, is the main test provider.

CBC studies typically yield three kinds of results. First are those that quantify both properties of the blood, particularly the cell mass or packed cell volume, commonly termed the hematocrit and the total hemoglobin content of the blood. Single analyte devices or spun hematocrit and hemoglobin are already waived by regulation and need no further consideration by the Panel.

Other results provided in a CBC are counts of the formed elements of the blood including the erythrocytes, leukocytes, and the platelets. To

date, no test that directly enumerates formed elements has been waived by FDA. Instruments providing these results are a major focus for the Panel discussion for today.

We will not be discussing today for waiver testing the report indices such as mean cell volume and mean corpuscular hemoglobin.

Differential cell counting goes beyond the CBC to discriminate and count various subpopulations of cells present in peripheral blood. A differential cell count typically yields results for the five main classes of leukocytes. Some instruments provide only aggregate results that merge some cell types, for example, pooling neutrophils, eosinophils, and basophils to report granulocytes or pooling lymphocytes and monocytes to report mononuclear cells. Instruments providing either the fully specified or the less detailed versions of differential cell count are a major focus for discussion today.

We will not be discussing tests for additional types of cells with physiological or pathological implications or tests for cell phenotyping via molecular markers.

Regulations and FDA guidance provide key

criteria for determining whether a device should be cleared for use in waived laboratories. Test simplicity is one of these, and you've heard much about this already from Carol Benson.

Another major requirement is that there shall be an insignificant risk of an erroneous result from the test as performed in waived laboratory settings. This requirement has two aspects. First, the test should yield accurate results when performed correctly. Accuracy in the general context of CLIA waivers has been discussed already by Ms. Benson and Marina Kondratovich. Estelle Russek-Cohen, who follows me, will present more information about accuracy, specifically in the context of CBC and differential cell counting.

The second aspect of insignificant risk is that the test should pose no unreasonable risk of harm to the patient if performed incorrectly. Such risk is a complex topic related in part to the accuracy of the test result and also related to the intended use and clinical expectations for the test. Much of the rest of my presentation will address this topic.

The basic blood cell classes are morphologically defined, and the recognition dates to

Ehrlich's development of standing techniques in the late 1800s. Ties between morphology and the roles for the various cell classes in health and disease persist still today. Information from the cellular elements in peripheral blood helps providers answer clinical questions ranging from generic to highly focused and from routine to critically important.

Manual or visual counting, as has been done for several decades, always remains an option if the need for it is recognized by testing or clinical personnel. There are well-known strengths and weaknesses with manual counts just as there are with automated counts.

Since CBC and differential counts yield a collection of measurements, rather than a single reported value, some guards against erroneous or misleading results can be implemented through cross-checks and correlations among the measurements looking for inconsistent or unexpected results if the testing personnel or the end user of the test result is alert to them.

Microscopy-based visual methods are still the primary reference for accuracy of the CBC and differential cell count. FDA has recognized Standard H20-A2 published by the Clinical Laboratory Standards

Institute for use in evaluating differential cell counters. In clinical practice, the strength of visual methods is in the ability to make subtle distinctions between cells allowing confident interpretation of unusual or unexpected findings.

However, visual methods require much effort especially for precise counting of cell types that are present in low numbers. This is because the precision of any counting method depends on the number of counted events.

Each scattergram on this slide plots duplicate cell counts to show the correlation. Neutrophil counts are on the left and lymphocyte counts are on the right. The top two frames show 200 cell visual counts and the bottom two frames show 10,000 cell automated counts. It's clear that the duplicate count agreements are tighter for the 10,000 cell automated counts than for the 200 cell visual counts. In addition, the agreements between the neutrophils on the left are higher than for the lymphocytes on the right, whether due to their high relative number or their ease of recognition.

It is notable that the accuracy of some automated differential cell counters has been validated using visual counts of 500 or even 800

cells per specimen. More often though, smaller numbers of cells are visually counted. For some new instruments, accuracy is checked solely against results obtained from another cleared, automated instrument.

As with manual methods, the automated measurements from peripheral blood counts fall into two distinct groups. Hematocrit and hemoglobin are single-valued bulk measurements that prove relatively easy to automate. These are the hematology measurements for which some devices are already waived by regulation.

It's harder to automate total and differential cell counts. Some early methods relied on analyzing images of cells captured on slides. Those image analysis methods still have a place for some applications, most work now relies on much faster methods that detect and characterize particles flowing in tightly controlled streams. The ability to characterize a large number of particles in a short time is the principal advantage of automated methods. All automated methods rely on cell-by-cell measurement of physical or chemical properties that are correlates of cell morphology though not the same as morphology itself.

Just as with manual/visual methods, pre-analytical and analytical challenges can complicate or degrade the performance of automated cell counters. Some, such as clots and hemolysis, chemical interferences and requirements for an appropriate anti-coagulant, are common to many blood-based assays whether waived or not and need at least as much diligence from personnel to recognize or avoid them in hematology testing. Hematology results can be affected by small degrees of clotting that do not affect many other tests. Some analytical challenges, such as antibodies causing autoagglutination or rouleaux formation, are hard to recognize and subtle in their effects.

Altered cells, such as microcytes and misshapen or fragmented erythrocytes can further complicate analyses as can cell types that normally are rare or altogether absent. Sophisticated instrumentation can often help recognize and deal with these problems, but along with such sophistication may come heightened expectations for expertise in the user.

Visual and automated counters use fundamentally different signals to do their work. On the left are the major features used for visual

morphological classification of cells, and examples of features used by automated cell counters are on the right. Both technical approaches rely first on identifying individual cells to counter classify. Visual events might include overlapping cells that must be discriminated or rejected, and automated counters also must detect and handle coincident events from doublet or higher order particle aggregates.

Human readers integrate features such as size, shape, color and structure to classify cells. The automated instruments combine various electrical or optical signals to count and classify cells.

The signals and classification algorithms used by automated cell counters do not reproduce the full range of particle discrimination that the eye and brain can provide. The various instrument designs represent tradeoffs between analytical completeness and test costs. Using just leukocyte analysis as an example, some instruments report only the total leukocyte count. Differential cell counts will usually, but not always, be performed together with a total white blood cell count so that absolute and proportional results are reported.

Some systems will report a three-part

differential count with neutrophils as one class, lymphocytes as a second, and combination of monocytes, eosinophils, basophils, precursor cells and plasma cells, as a third population termed M I D or MID.

Another form of three-part differential count reports granulocytes comprised of neutrophils, eosinophils and basophils as one class, lymphocytes as the second class, and monocytes as the third.

The most advanced instruments report all five main leukocyte types plus variant and pathological cell forms.

It is self-evident that instruments reporting only a few cellular analytes do not provide the comprehensive analysis of formed blood elements that is available from a complete automated analysis, especially one supplemented by manual, visual examination of a blood film when indicated.

Listed here are some conditions for which the blood count may be normal, but examination of the peripheral smear will suggest a disorder to an informed observer. The essential thing for each specimen is to match the rigor of the test with the clinical need, whether that need is fully appreciated initially or not. Most automated systems are

designed to do this through a flagging system. Flags draw attention to specimens because the number or the distribution of classified events is outside tolerance limits or because the instrument detects events of a kind that it is not designed to classify. In either circumstance, an appropriate next step is to prepare and examine a peripheral blood film, activities that are not suited to a waived test setting.

How often are peripheral blood film examinations performed? A study published recently by the College of American Pathologists for 263 hospitals and independent labs found that more than 1/4 of automated complete blood counts, including automated differentials, went on to some form of manual review. Among the laboratories in the lowest decile for blood film exams, still nearly 10 percent of specimens had a peripheral smear examination.

A Canadian group's early study concerned automated testing of outpatients alone and found that 35 percent of 1600 consecutive specimens were flagged. Three-quarters of these had a corresponding abnormal finding in the blood film. The Canadian authors noted that a left shift and immature granulocytes were the most common findings with such

flagged specimens, and they discounted the significance of these findings given the expectation that they are commonly accompanied by neutrophilia or leukocytosis.

One might hope that using CBC and differential cell counters in precisely defined clinical settings would help to limit the range of issues that testing personnel might encounter. However, this is not assured. Given the long history and varied uses of these devices, it is not surprising that the device regulations mention the analytes and some aspects of methodology, but they're mute as to the clinical context of their use. As a result, instruments are cleared for professional use and would be for waived use without regard to the specific clinical questions they are used to answer.

Hence, applications of CBC and differential cell counters range from routine screening exams for patients of any age to focused use in the differential diagnosis of ill patients, to monitoring for ill effects of treatment, manifesting, for example, as decreased cell counts and to monitoring the course of disease and the effectiveness of treatment. All these kinds of applications are prevalent in outpatient settings such as might be