encountered with waived testing.

A key to successful testing is ensuring a match between the complexity of the test, the expertise of the testing personnel, and the expectations of the healthcare providers who use the results.

Appropriate use of reference ranges is an important aspect of successfully applying the results of blood cell counts. The physiologic variation in certain blood cell counts exceeds that of many blood chemistry analytes, and the profiles of expected results can vary further across normal populations and across patient groups. It has not been practical for device labels to address a multiplicity of reference ranges. And so CLIA-certified laboratories must establish or verify reference ranges for the population tested. It is appropriate to consider whether or how waived laboratories will obtain suitable reference intervals. Similarly, the question of how the waived laboratories should evaluate and follow up results falling far outside an appropriate reference range needs consideration.

FDA recognizes the potential for significant benefits that waiver might bring for CBC and differential cell count testing of outpatients.

First among these is rapid availability of results that could help guide a diagnostic lookup at first contact or prompt immediate modification of therapies in response to hemologic signs. A related benefit may be the use of a wider range of testing locations and personnel for CBC and differential cell counting that are required for moderate complexity testing. These have caveats concerning the likely need for follow-up testing or potential challenges in training or retaining test personnel.

Issues of adequate test accuracy, an informed review, or follow-up of test results are part of the discussion framed by FDA's questions to you today.

The establishment of waived hemologic testing is likely to have large effects. The volume of CBC tests order or provided at an ambulatory care setting, primarily in physicians' offices, was nearly 88 million in 2004. This is about four times the volume of hematology testing reported for hospital outpatient departments in 2005.

Recent publications on alternative pathways for ambulatory care including convenience care or retail clinic settings that will rely on use of waived laboratory tests cite the potential for rapid

expansion of such a practice model. Along with the potential for greatly expanded hematology testing, it is important to consider the degree to which changed testing patterns and staffing expertise may impact the cross-checks, correlations, and expertise that are now brought to bear on CBC and differential cell counts.

The requirements for waiving in vitro diagnostic devices are fourfold. Satisfy the requirements for simplicity, analytical accuracy and insignificant risks from erroneous results, all set the stage for preparing adequate labeling. The FDA requests your input particularly on the ways by which CBC and differential cell counts might meet the first three of these requirements. Thank you.

DR. ADCOCK: At this time we'd like to have Dr. Russek-Cohen present.

DR. RUSSEK-COHEN: Thank you. Good morning. My name is Estelle Russek-Cohen. I'm a team leader in the Division of Biostatistics of the Center for Devices and Radiological Health. And today I'm going to continue with statistical issues, but I'm going to focus on issues specific to CBCs and the automatic differential cell counting devices.

First I'm going to give you a little bit of

background and terminology, and then I'm going to talk about establishing "accuracy." Accuracy is in quotes because as you've seen before, it's in the context of the guidance. I'm going to talk a little bit about the study conditions associated with the waiver study, talk about allowable error, talk about some of the issues that have been alluded to by Dr. Becker with regard to reference ranges, what kind of performance we actually have been looking for in these waiver studies and then a little summary.

First, I'd like to contrast the typical 510(k) versus the waiver. In a 510(k) study, the sponsor often comes in and compares himself to an already marketed device for a similar intended use. We call that establishing substantial equivalence. With a waived device, we're asking the sponsor to compare themselves to a comparative method, to in a sense establish accuracy. 510(k) submissions, typically they're in the hands of a laboratorian, and for a waived device, we're asking that the CBC assay be demonstrated in the hands of a non-lab health provider.

As mentioned earlier, some analytes have been waived essentially by regulation, and so I'm not going to focus today on hemoglobin or hematocrit but

rather focus on aspects of cell counting.

So I'd like to reinforce some concepts that my colleague talked about on this notion of imprecision and systematic bias. The fact of the matter is most lab assays have some inherent imprecision or variability, but a user might have the option of running samples in duplicate and averaging, and in the process of doing so, you tend to reduce variability.

Systematic bias would imply a new assay yields incorrect values on average, and if an assay has systematic bias in the rigorous sense of the word, it cannot be accurate. Averaging over multiple runs of the same assay wouldn't be sufficient. However, our guidance allows for assays that have negligible bias.

Traceable methods, this has also been discussed previously, but they're methods traceable to references of higher order. It can be certified reference materials, a reference measurement procedure or a network of reference laboratories. The guidance calls for traceable method if a reference method is unavailable, and the context of CBCs will primarily get a focus on a reference measurement procedure.

Establishing accuracy. Manual counts are the recognized reference method in the context of today's discussions. Erythrocytes, leukocytes, WBC differentials, whether it be a three-part differential with lymphocytes, monocytes or granulocytes or alternative three-part differential or a five part or platelets, manual counts has historically been the referenced method.

Most people recognize that manual counts are noisy. They're imprecise. Sponsors may have the option of averaging over multiple manual counts or in the context of today's discussions, to show that a well-established CBC device is traceable to manual counts. They can do this by citing appropriate literature or conducting their own in-house study. The fact of the matter is if you can reduce imprecision of the comparative method, it's easier to pass.

A one-step design. Sponsors would have the option of doing manual counts in duplicate, triplicate, and if they're really ambitious, they can do it in quadruplicate, but it's logical to do it consistently across all the samples, and that average effectively becomes the comparative method. Then they would compare the waiver method result as it is

used on the label as typically a single value, and they would compare that to the average manual count for the same specimen. It's very labor intensive with 360 patient specimens.

An alternative two-part design would be to establish the lab CBC result as a good traceable method as described on the guidance. It may have very negligible bias. As I've alluded to before, the sponsor would have the option of establishing traceability, and we would suggest that they have 40 samples to span the measurement range of each analyte, and 40 is the number suggested in the CLSI document, EP9, for comparing two methods, and that's where the 40 comes from. They would have the option, since this is primarily for the purposes of establishing traceability to average replicate lab CBC results, and then they would need to develop an equation essentially that relates the lab CBC result to the manual counts.

Then once they have the lab method established and they've satisfied the requirements, they can then compare the waiver result against single values to the comparative method. The comparative method again would be the average of lab CBC results. The split sample would go to the lab

for analysis, and it would be 360 patient specimens.

This is a diagram that sort of illustrates the idea of, I guess, traceability. You can go from manual counts to the traceable method to the waiver method, and the sponsor might have more than one option.

One would have 40 samples that would go from manual count to traceable, again motivated by CLSI document, and they would have to do it analyte by analyte, and then they would pose for the 360 that's -- guidance, to go from traceable to the waiver method. Alternatively, they could do 360 patient specimens and go from manual count directly to waiver method.

As discussed before, what we typically see is what we think of as a split sample design. It could be two venous samples if the waiver method is for venous blood samples, or alternatively they could use a split sample -- well, paired sample design where you take a fingerstick blood sample from a patient and a venous blood sample, but the idea is that the venous blood sample is done in the hands of the professional, and the waiver method is done by the waiver method users at the waiver site.

The waiver study should mimic real clinical

conditions. We'd like to see the device use integrated into normal work. We'd like to see a minimum of two weeks but two to four weeks is suggested. It should include three or more sites. These sites should be reflective of real world use. They should include nine or more users with no more than three per site, and the users should not be trained laboratorians.

Study conditions. The user should be aware of safe handling of blood specimens. Training, they have access to the quick reference instructions, a package insert, and they're allowed to provide a 1-800 line if that's going to be offered when marketing. The training should be consistent with instructions under real world use.

Quality control, it should also mimic real world conditions. For the comparative methods, the results should be consistent with state and local requirements. It's important to note that there are typically no state and local requirements for waiver methods in a waived lab. QC materials need to be recommended or provided by the sponsor.

The specimens need to span the measurement range. So, therefore, sponsors should carefully consider the types of study sites that they elect to

choose so that they can find abnormal specimens as well as normal ones. Up to one-third have to be contrived or spiked specimens at most, and there are about 120 specimens per site and at least 360 specimens overall.

My colleague described the idea of allowable total error, and one of the things she pointed out is CLIA 88 suggests some acceptable limits for several analytes. So allowable total error, I remind you that hemoglobin and hematocrit devices have already been waived. And the acceptable limits based on CLIA 88 is being within 7 percent, hematocrit as being within 6 percent, white blood cells being within 15 percent, RBC, erythrocytes being within 6 percent. Platelet count should be within 25 percent.

There's a recent review article from a group in Europe, and they used the term, state of the art. I regard it as a literature review of what's really out there in the context of these kinds of devices. I reiterate the CLIA 88 requirements on the slide, but for white blood cells, recently reported ranges for the better devices are well within those CLIA 88 limits, and you can see that that's true across all four of the analytes on this slide, but I

will also note that for these four, it's assuming the same allowable total error expressed as a percentage over the entire range.

Limits of erroneous results, the definition, patient results inside the zone are going to pose a risk to patient safety. In a sense, it's a concept defined in the Waiver Guidance, and really we would like your clinical input.

Clinical considerations with the allowable total error and the limits of erroneous results. The indications and intended use populations for CBC and differential counts are very heterogeneous. The ATE and the LER should be specified to meet the most demanding intended use settings. The ATE and the LER might vary across the range of reportable values.

And so this is my colleague's diagram, but I think it's worth reinforcing, okay. Essentially you have the comparative method along the X axis. You have the new method along the Y axis, and you could do an alternative plot, as has been suggested by one Panel member, where you could look at the difference between waiver method and comparative method. The information is roughly the same. But we would expect at least 95 percent of the subjects to fall within the green lines that you see up there,

the allowable total error region. Of course, we would welcome more, and out of 360 subjects, we would not expect any to fall within the limits of erroneous results outline in the red region.

Allowable total error, white blood cell differentials. When we look to CLIA 88, it says what the purpose of proficiency testing, when you look within your peer group, you have to be within three standard deviations. This criteria did not seem particularly appropriate for an allowable total error criteria.

I refer back to the same article I cited before. Again, it's a European study. Again, it's state of the art as defined by the authors, but they also talk about recently reported intervals in terms of the best lab devices, and on the other hand, we are asking the panel to comment on allowable total error. I do want to point out a couple of things on the slide.

For monocytes, it's all the way up to 58.7 percent. Eosinophils goes up to 37, and for basophils it goes up to 155 percent. And as a statistician, I would say, oh, my God. So -- but you need to think about what's going on here. Those are relatively rare cells in the grand context of these

devices, and being off by a certain percentage may not have clinical ramifications especially if you're down in the reference range. Okay. So it strongly suggests that when you do an allowable total error, that you think carefully about the range values, and it may not be one slice fits all over the entire range, and I think that's the reason these percentage are so high, because basophils are very, very rare in the vast scheme of things for white blood cells.

Reference intervals. They're typically the middle 95 percent of values you're likely to see with apparently healthy subjects. They may vary even in healthy subjects by age, gender and altitude. If we look at the clinical Lab Standards Institute document on establishing reference ranges, C28-A2, they suggest 120 subjects to establish a reference interval, and that presumably needs to be done for each age, gender, and possibly if you're in Denver, you might need a different reference interval. And the one question we would have for the Panel is, how likely is establishing a reference in a waived setting?

There are potential other options that the Panel may wish to consider. A waived setting could use values that are cited in the 510(k). Sometimes

these in turn refer to cited references and sometimes they have real data. Alternatively, they can use values from large surveys. The CDC produces a survey called the National Health and Nutrition Examination Survey where the values for a CBC and automated differential cell count are published by line data, however you decide to break it up, or you can basically use literature, for example, well-established hematology textbooks provide reference intervals. These are typically calculated using a well-established lab CBC counter, and it's worthy to note that if an assay is a little noisier, those reference intervals probably need to be made a little wider if they really constitute the middle 95 percent.

Performance. We ask the sponsors to find low, medium, and high ranges for each analyte. We ask that allowable total errors and limits of erroneous results be predefined. As noted by my colleague, these are not just logistical considerations. These are serious clinical considerations that you need to come in with and you need to have that up front. These analytes have been very well studied. It's not likely to present something totally novel. Clinicians should have some

idea. The samples do need to span the measurement interval and should include abnormal specimens. The sponsor must pass for each analyte.

One part of performance is to capture bias, because if you recall, one of the things we are concerned about is systematic differences between the waiver method and the comparative method. We ask that that's done overall by study site, by low, medium and high ranges, and we ask that the sponsor consider using regression analyses appropriate to the data set. And what is typically done, sponsors will then provide scatterplots and regression lines, and we also ask them to evaluate systematic bias at medically important concentrations, and we are expecting negligible systematic bias.

The second part of the performance criteria is at least 95 percent of the waiver method values is going to fall within that allowable total error region; 95 percent two-sided lower confidence bound has to exceed 92 percent, and we expect similar percentages inside the allowable total error region for both low, medium and high ranges. We expect none of the values to fall in the limits of erroneous results, and we expect the 95 percent two-sided upper confidence bound to be less than 1 percent.

So, in summary, FDA would really like the Panel to consider the following when answering our questions: what the allowable total error ought to be for white blood cell differentials, what the limits of erroneous results ought to be for all CBC analytes and how reference intervals should be handled. Thank you very much.

DR. ADCOCK: Ms. Bautista will provide a summary of the information from the previous speakers.

MS. BAUTISTA: I will wrap up the presentations that we just had. I have two points that I would like to bring out.

The first point would be risk and benefit. Of course, we know the risk for the waiver of these types of devices will be to help the physician and the patient as far as the convenience of having the results available in a more immediate timeframe so that they can make a diagnosis, but I think we first need to look back at what do we mean by convenient to the patient, and then we look back at how fast the results are, and sometimes they look at the costs. But the issues that we have to think about is first of all, results to the patient, I mean for the physician in a more expeditious timeframe. Is that

really the truth? I mean, we're going to have to look at that because if the patient goes in and have this test done, we're assuming that the physician is there. In a waived setting, the physician may not be there. There's no requirement in a waiver setting to have a physician there to read the results or even analyze the results. These are all based on the people that are doing the testing.

Dr. Becker just talked about 30 percent to 50 percent of the patients may have to have re-flex tests based on a differential cell count. That's not going to be available in a waived setting. So then that patient now has gone from being convenienced to inconvenienced because now they have to go to a laboratory and be retested.

So these are things we have to think about when we're looking at how we're going to decide if this is something that we should weigh.

Also, we have to look at the risk for error. Are the results that are going to come off of the analyzer correct? Can the person that is analyzing these results pick up the errors that may be inherent within this assay?

In the laboratory, we have large analyzers that have more assays available for analysis, and

these assays, like was talked about before, indices, we have scatterplots. We have the differentials and things like that, that back up the professional. We don't have anything backing up the non-professional. If the professionals need help, then isn't it to assume that now we need extra help for the non-professionals, and these are things that we all have to consider when we're doing this. We want to consider the risk to the patient, and this is our main concern. This is why this meeting is so important because we want to make sure that we have addressed these issues.

And the second thing I want to bring up is define parameters to meet the waiver criteria. Evidently, we haven't defined the criteria, and the hematology device does not fit neatly into our waiver program because we are still having problems. There are a lot of inherent risks. There are a lot of errors that we have to figure out how we're going to go about deciding what is the amount of risk we can accept as far as in these devices. So these are issues that we're asking you for your input on and your assistance to help us decide how to go about waiving these devices or even if they should be waived.

I appreciate your time and will entertain any questions from any of our members that spoke in this timeframe.

DR. ADCOCK: I believe we'll go ahead and take questions at this time. Please speak directly into your microphone.

DR. BULL: I can see that before the day's over, the Panel members are going to be requested to provide some clinical input on things like allowable total error or limits for erroneous results. And I, for one, am having a great deal of difficulty even understanding the concept. Slide 22 of the presentation by Ms. Estelle Russek-Cohen brings us back to an illustration that we've had now presented I think three or four times, and I guess the red lines indicate regions where a result in laboratory parlance would be described as totally ridiculous. What I don't understand is what are you going to do with results that are outside the green lines but not yet inside the red lines? It seems to me that you're asking us to put a fixed limit on outlier assessment. Why would it not be just as reasonable to do some sort of analysis of the outliers, those that are beyond the 95 percent limits, and specify that outliers in excess of a certain number of standard

deviations, assuming we're dealing with parametric data, are just simply unacceptable?

DR. RUSSEK-COHEN: Well, essentially you can define it that way in the sense that you could make those red lines incredibly close to the green lines if that's really what you felt was appropriate.

DR. BULL: No, but my problem is that I don't want a line because that line's going to be different for different clinical conditions, and I don't see -- and it's going to be different for each of the analytes, and --

DR. RUSSEK-COHEN: Well, I agree it's different for each analyte. It has to be.

DR. BULL: But it's also going to be different for each clinical condition, and I don't see how we as Panel members can be expected -- I mean where did this concept come from? I never heard it before.

DR. RUSSEK-COHEN: Well, it's in the Guidance, and it was suggested in part by the CLIAC Committee. I believe it was a three-agency committee that sort of said, in a waived setting, you really don't want outrageous observations, and that's essentially what --

DR. BULL: We don't want outrageous

observations, but I don't see how we can put a line beyond which it's outrageous and just inside of which it isn't. That's, that's my problem.

DR. GUTMAN: Well, I mean you're welcome to make other suggestions on approaches here. The notion here with the allowable error is that it's elastic. Obviously if you make the allowable error immense, then everything is waivable, and if you make it incredibly tight, then nothing is waivable, and the intent here was to try and find a place where there was a reasonable tolerance for error for whatever product, whether it's a CBC or it's another product, where there was more good than harm. So the notion here is, you know, if you're very conservative, then you would want the green lines to be --

DR. BULL: I don't have a problem with the green lines.

DR. GUTMAN: Okay.

DR. BULL: It's the red ones that I have a problem with.

DR. GUTMAN: Well, okay, the red lines, you can tell us to get rid of the red lines or you -- the red lines, the red lines -- the notion was that there's a, you know, real harm, there's an element of

harm that, you know, it's like a place where there's area that you can tolerate, and then there's a place where there's area that you just can't tolerate, and, and again, you can make the red lines very, very close, in which case perhaps nothing would pass, or you could make them very far, in which case everything would pass.

DR. BULL: But you understand --

DR. GUTMAN: But what we're asking you to do is -- we realize this is tough and maybe there isn't an answer, but this is tough, but actually we're asking for your best estimate, and we do recognize there are multiple analytes. You have to for each analyte pick the worst-case scenario. You have to assume, you know, in the waived setting it will be assumed broadly. You can't assume the best-case scenario. So you have to think of what you would clinically worry about the most, and that has to be the criteria you recommend to us if it's even possible to recommend it to us.

DR. BULL: That's my point. You've made the assumption that it is possible, and I'm questioning whether that's true because a dot that is just inside that red line as opposed to a dot that's just outside the red line has to have some sort of

clinical justification, and I don't understand what that clinical justification would be, and it's going to differ for each condition that you're analyzing, but maybe I'm the only one on the Panel -- it's just that I'm warning you that if later in the day you want me to put a number on that red line, I'm going to say I don't think it -- the red line should be there, and it should be replaced by some sort of a continuous analysis.

DR. RUSSEK-COHEN: Well, it could be, and that's something that you could potentially recommend.

DR. KOST: May I ask, as long as we're on the subject, could you explain slide 30 as well where you -- and also tell me if the premises parametric or non-parametric confidence interval?

DR. RUSSEK-COHEN: Actually it's a confidence bound on binomial proportion. You're either in the allowable total error or you're outside. So there's really -- I don't know if you want to call it parametric or non-parametric. It's based on a binomial. There's no inherent assumption or normality here if that's your concern.

DR. KOST: What is the 92 percent then? How did you calculate that?

DR. RUSSEK-COHEN: Basically you have 360 observations, and 95 percent fall within, all you can say is in the future, you might not expect less than 95 percent. I think it's 92.8. That's below the confidence bound for that proportion. So it's not terrible parametric in that sense. And there are devices. The Guidance can say it can be higher if the clinical ramifications say it ought to be higher.

DR. KOST: Okay. So if I understand you, 95 percent would be the data on the table.

DR. RUSSEK-COHEN: That's exactly right.

DR. KOST: 92 percent would be the future expectation of meeting that same criteria.

DR. RUSSEK-COHEN: Yeah, and sponsors may actually have to have --

DR. KOST: 92.8.

DR. RUSSEK-COHEN: -- something that operates better in order to guarantee they have power essentially to exceed that 92 percent.

DR. KOST: Okay. Thank you.

DR. KULESZA: I have a question to state that I don't know maybe help us because I'm having similar problems with the red lines. Waiver by regulation, how do we waive the hemoglobin single analyte instruments? Is there any analogy that can

be drawn? I am thinking in particular with that instrument says hemoglobin is 4, that is obviously a catastrophic value. Is this value correct or not and what do we do in that clinical situation? How was that considered at the time of waiving those instruments? Was it?

DR. GUTMAN: Well, the waive by regulation was, you know, I'm not sure it was a mathematical determination. I think it was, again, Judy will have to quality control me or someone who knows the -- of the CLIA program more than I do. I think it was just based on the fact that they had such an established history. So we reviewed these as substantially equivalent. So we determined them substantially equivalent. We actually don't start to worry about, maybe we should but we don't, because it's not actually a regulatory possibility to worry about any of these parameters once it's shown to be substantial equivalence, then come hell or high water, it's waived.

DR. KULESZA: I see. So this LER concept is actually established de novo for the purpose of --

DR. GUTMAN: Yes. I'm not sure it --

DR. KULESZA: -- safety --

DR. GUTMAN: I'm not sure if the selection

of the categories for waiver were actually determined by Congress or were they determined by HHS.

DR. NG: We're spending a lot of time grappling with the idea of trying to set up what would be an allowable total error, and I was very interested in your slide about Plebani's study. Am I correct in understanding he generated this data from CAP surveys? Is that --

DR. RUSSEK-COHEN: No, he did a literature review as well as perhaps surveys. I don't know whether he specifically did CAP because frankly from Italy, and so I don't know exactly which PT results he examined. He did a broad literature review.

DR. NG: And if, in fact, these are PT derived data, I'd like some information on, you know, PT derived data is usually using fixed samples.

DR. RUSSEK-COHEN: That's correct. And this was a range of values from various studies and he didn't allude to it --

DR. NG: Which every time I try to calibrate my instruments using a fixed sample, I get a lot of criticism about how fixed samples don't behave as native cells. So I'd like to know what, in fact, is the relevance of using PT derived error in trying to --

DR. RUSSEK-COHEN: They're not all PT derived. I do believe he had a literature review of various studies that had been done that would direct --

DR. NG: Fresh patient samples --

DR. RUSSEK-COHEN: I believe so.

DR. NG: -- instrument to instrument.

DR. RUSSEK-COHEN: Yes.

DR. KOST: Is this slide 19 and 24 we're talking about?

DR. RUSSEK-COHEN: 19 is where I was focused.

DR. KOST: What -- could you define what you pulled as ranges in that slide. How do you define range?

DR. RUSSEK-COHEN: He said he basically looked at several of the best CBC analyzers out there, and what they were reporting is their -- well, as the percentage deviation from I guess manual counts. There were a number of studies that he cited. It's a broad literature review. I think the sole point of this is that the CLIA 88 stuff is obtainable now with many devices that are out there, and that's all I was trying to say, and it's just a literature review, and I think you all know that

literature reviews are incomplete.

DR. WANG: I happened to have brought that article with me if anybody wants to read it.

DR. SANDHAUS: I'd just like to make one comment. We've heard several times this morning that hemoglobin hematocrit is already waived. So we really won't be addressing that specifically, and most of the discussion and questions this morning have dealt with the white blood cell count and automated differential count, and so far today we really have not specifically mentioned platelet count, and I think as we consider waiving CBC instruments, we need to specifically address platelet counts as well in our discussions.

DR. ADCOCK: And I would just like to ask the Panel members if they could indicate that they have a question and wait to be called on. We've got quite a few questions. Yes, Mr. Bracco.

MR. BRACCO: My question has to do with the fact that the comparative method that you spoke about was manual counting, and I'm just curious as to whether or not we should be using as the comparative method the cell differential device, cell counting differential device, used in a professional setting versus the device used in a waived setting versus a

manual count versus the device used in a waived setting.

DR. RUSSEK-COHEN: Repeat that one more time. This is the diagram I guess, and you're asking if --

MR. BRACCO: Yeah, the comparative method you had as a manual count, and I guess in my head I've thought the comparative method would be that device used in a professional setting versus the device used in a waived setting. Is that incorrect to assume that?

DR. RUSSEK-COHEN: Do you want to answer that question?

DR. BECKER: There's a difference here between a waiver situation as to the waiver versus a 510(k) substantial equivalence -- and so I'm sure that either Marina or Estelle can put a finer point on what I'm saying, but the crux of it is that you need to have some kind of reference method or something which is traceable back to a reference method in some explicit sense as the basis for evaluating the performance of the device you would now like to see waived. So unlike the circumstance where you might have allowed in say a 510(k) setting, device A is marketed, B is equivalent to A. So it

goes C is equivalent to B, B and so forth. Here you need to have some way of being able to ground this back onto a method which you're confident gives you solid results.

And so I'll turn it back to Estelle in a moment, but what this basically is suggesting to me I think, okay, is that you can either go back to the manual method for the purpose of your comparison in a waiver study and has already been talked about before, recognizing that that can be noisy, you might want to have lots and lots of replicates to make sure that you've been able to squeeze out the imprecision that might be associated with that method. Or you might be able to use a comparison to a device which itself has been taken back against that comparison method so that you're confident about its performance. So that would be the idea of using the traceable method against which your waiver would then be compared. I hope I got that right.

MR. BRACCO: Thank you.

DR. ADCOCK: I have a question about the number of participants in the study, and frequently it's been cited that 360 patients will be evaluated. My concern is that we're looking not just at one analyte but at multiple analytes, and I'm wondering

if there should be a certain number that are evaluated per analyte.

DR. RUSSEK-COHEN: Well, there has to be 360 per analyte minimum, and what we've seen with companies that have come in with a panel of analytes is in order to meet the range of both low, medium and high values, they've exceeded 360.

DR. ADCOCK: So to be perfectly clear then, we would have to look at 360 per platelet count --

DR. RUSSEK-COHEN: Correct.

DR. ADCOCK: -- for each of the -- and how would that pertain to the differential then?

DR. RUSSEK-COHEN: They need 360 broken down exactly the way the device would report it. And so companies have exceeded 360 in order to satisfy low, medium and high with the chanalite (ph.) because different patients may be high on one and low on another, and as a result, it may exceed 360; 360 is minimum, and what we've done also to compensate in the sense with the 360, 0 percent falling within the LER, we say that the upper confidence bound should be less than 1 percent, and since you don't want a company feeling jeopardized because they've collected more than the 360, you also say that 92 percent is the lower confidence bound. If a company comes in

with 410 values, the observed performance could actually be like 94.something and they still exceed the 92 percent, and they've got a lot to be waived. So the 92 percent is probably the harder one, but everybody would worry a lot if you weren't very close to the 95 percent. You actually observe -- this allows -- everything comes with errors you'll discover. Assays come with errors and statistics come with errors. So we'd like to see 95 percent, but if you had a very large number of patient specimens, because you're trying to meet this low, medium and high range across all these analytes, we're going to hold you to the 92 percent lower confidence bound, and that usually means that the percentage ought to be pretty darn close to 95 percent, and so if it winds up being 94.5 for one analyte, that's probably not going to raise as much of a concern. If it goes much below that, you're going to have trouble meeting the 92 percent lower confidence bound.

DR. ADCOCK: And then given that the analytes have to -- or the results have to span the range, are there any requirements as to a percentage that have to fall within those various levels?

DR. RUSSEK-COHEN: We're suggesting similar

percentages. So we ask the company to think carefully about how those ranges prove to find before they come in to do the study. And so they should know something about the general practice that they're working with, and that's why we're saying it's so important to be careful what kind of study sites you pick because you're going to need to get some abnormals so you know that maybe hematology practice might have certain kinds of values and a family practitioner might have a very different set of values, and when you pick the study sites, you need to think about that.

DR. ADCOCK: And then is there any requirement by the FDA that certain age ranges are evaluated?

DR. RUSSEK-COHEN: It depends on the intended use of your -- I don't think it's spelled out you need 360 adults, you need 360 children, but it's something you would have to think about. Is that a concern? Is that an issue? I am a statistician. I can't tell you how important it may be. Other people may say it's very important, but I think the Panel needs to weigh in on that consideration.

DR. BECKER: So as a brief comment, I'm not

aware of us having explicitly called out gender or age as a specific point of concern in looking at the methods' comparison. We like to make sure that they are both represented, but I don't know that of any circumstances in the 510(k) realm where we've specifically indicated that you have to document performance that is tied to strata of those variants.

DR. NORBACK: I have a question. I want to also address the concept of a limit of erroneous results, and it seems like the purpose of that is to make sure the instrument will not give a result that is harmful to the patient, and it seems like your approach is to base your conclusion on whether any limits of erroneous result, however it would be defined, would not come up when we do 360 samples. But I think we could challenge the instrument much more rigorously before this clinical study by challenging it to identify samples that it's almost bound to give erroneous results on like chemoli samples or clotted samples or samples with, you know, very low platelets or even very high platelets, and really the test is can the instrument give results that are accurate and have allowable total error, not so much in a statistical sense but in an empirical clinical sense.

For example, low levels of neutrophils and platelets and lymphocytes are important, and the allowable total error when you think of it in terms of absolute numbers rather than relative numbers, I don't know, I will just propose that we should be able to detect neutrophils plus or minus 200 neutrophils per micrometer when it's a very low number, but that number is not so important. 200 is not important when we're analyzing neutrophils in the normal range or in the high range. So the first thing we should do is just challenge the instrument to see if it can do the results that are clinically relevant. And that would be my approach to defining the allowable total error and the limits of the erroneous error.

DR. RUSSEK-COHEN: A lot of the challenge studies could be done, but they're often not done at the waived sites. So those kinds of studies could be done but --

DR. NORBACK: No, it would have to be, it would have to be before the clinical studies.

DR. RUSSEK-COHEN: No, I agree.

DR. NORBACK: And the first question is can the instrument even do it before we allow it to look at 360 samples that are not going to be as

challenging as the examples that we can make up.

DR. RUSSEK-COHEN: Of course, we could ask the -- I don't know if Bob want to --

DR. BECKER: I think we've asked that in one of the questions that you'll have a chance to consider later today. I believe the question that you're asking is that we would want to see the instrument challenged with respect to difficult specimens, some of which might have pre-analytical questions that would cause a problem, some of which might be clinically outliers that you'd want to make sure that there's not a mis-reporting coming back, and this can be looked at in a couple of settings. It could be looked at in the way that the instrument is originally cleared for professional use, as just part of the 510(k) process. One of the questions that we have is whether this needs to be looked at more specifically in the context of the waiver setting as well.

And so we're hoping that some of your considerations later on will help to tease that out, whether the studies might need to actually look at these questions in a setting beyond the way in which the instrument might have been initially evaluated for professional use.

DR. NORBACK: So I think my simple question would be are we allowed to define -- well, I guess we are. Are we allowed to define the allowable total error and the limits of erroneous results and then challenge the instrument to see if it can meet those in a setting other than this clinical trial of 360 specimens?

DR. BECKER: Well, we're interested in recommendations that might go in the direction you think is appropriate.

DR. KONDRATOVICH: I'd just like to add to that. When we reviewed the submission for professional use, we challenged the device exactly as you're saying. We challenged it in all different areas with all different disease states and so forth, but this is for a professional setting. Once it goes to the waiver setting, all of the backups that are available for the professionals are not there. So, therefore, we don't go back and recheck everything that we've done professional simply because that's already been done.

DR. NORBACK: Well, my comment would be that the instrument will have to be capable of identifying samples that it cannot give results on.

DR. KONDRATOVICH: Yeah. In a professional

sense, that is done, but what I'm saying is that once it is cleared for professional use, it's different than in the waived setting because in the waived setting, you don't have the expertise to follow up, and you're going to have errors that are going to come up, but those are errors that the professional user is able to identify, which is different in the waived setting.

DR. NORBACK: But since we don't have professional users with the waived instrument, isn't it appropriate to insist that the machine itself identify situations when it cannot give accurate results?

DR. KONDRATOVICH: Yes.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: Yeah, just one. Back to the limits of erroneous --

MS. BENSON: Could I just answer her question a little more? I think that we expect some of those things to be done in our flex studies when we stress the system, and we would like to look at those studies and what does the instrument do in those situations.

DR. NORBACK: I appreciate your answer. I guess it's a yes.

MS. BENSON: Yes.

DR. SANDHAUS: My question is, is there a requirement to establish limits of erroneous results for non-waived methods, moderate complexity, and high complexity testing? So this concept only applies to waived methods.

DR. ADCOCK: Dr. Ng, did you have a question?

DR. NG: Yes. I'm sorry. I was just going to make a comment that I would probably insist that this method be challenged with challenging samples in the waived setting. I would definitely insist on that because I can guarantee, number one, I would like to know if the person doing the test can even understand what that code means. Number two, I would like to know what happens to that device when they drop it or they put it under water and they run something and they get a flag on one of these challenging samples? Where are they going to get that answer?

I think what I want to see in the waived setting is that you're looking at the untrained user and their frame of practice and how it's going to relate to the accuracy of the test.

I also want to comment on the total number.

I understand the rationale for 360 samples, but put in the context, if we're running 88 million CBCs a year, if the prevalence of some of these disorders is on the range of 1 to 1,000, 1 to 10,000, you're not going to hit the native sample in the sample 360, which gets me a little bit more nervous about a waived device possibly being used at point of care by non-professionals.

DR. BECKER: These are all very robust considerations. One thing I'd just like to just make sure is recognized also is that the kind of specimen that can be obtained for use by instrumentation might vary with respect to its stability. For example, I might be looking at fingerstick specimens which would not be readily shippable or storable. We're talking about not pulling things back from banked samples, for example, as a means of trying to get at what might be challenging specimens.

So that along with the idea of being able to obtain challenging specimens to figure out how an instrument will handle them, we'd also be appreciative of recommendations about how to obtain such specimens for the various kinds of material that might be used upon the instrument.

DR. KULESZA: I just want to follow up on

that because I think that this is absolutely critical, and the choice of site that somebody mentioned is critical for that.

This instrument I would be extremely uncomfortable if one had contrived examples being tested to check the lower, upper not necessarily, but certainly the lower limits of the instrument being used, i.e., one has to go to a clinic that sees 100 ITP patients in 2 months and perform this study. And the numbers have to reflect it, and the samples have to be real, and I am sorry, but if shipping is not in the definition of a waived practice setting, then it is incumbent upon the sponsor to put the instrument and design the study in such a way that it reflects all the criteria that you were talking about in terms of dropping the instrument into the water or what have you. It just has to be done.

I think that also we might consider, as opposed to the limit of error, that whole concept, we could also think about panic and critical values because now that we are moving into a waived setting, those will be recognized differently, i.e., the potential harm to the patient with a result that is somewhat life threatening is very different than in a professional moderate complexity setting because that

almost guarantees a follow-up. So I think the facts that the instrument produce, there is a separate between the error as the clinical study is testing it, i.e., the instrument gives us what Dr. Bull called totally ridiculous result versus a result that may be true but is a panic value, and those do have to be handled differently and tested in the real life scenario. That will be my thinking about design of a clinical study for this setting. I mean, is that something that you have considered, Dr. Becker? To impose stringency that is of that order.

DR. BECKER: Well, it certainly comes into consideration. The main thing that I'm -- the main question, I'll simply indicate that we would like to have your input --

DR. KULESZA: I see.

DR. BECKER: -- rather than -- any way.

DR. ADCOCK: I believe we have time for one more question. Dr. Bull.

DR. BULL: We're on the topic of specimens, and these machines are going to be frequently used on fingerstick specimens, and I'm just wondering if the FDA has experience with comparative method studies utilizing fingerstick specimens on anything because that's going to be a really big problem for any

comparative method that I can dream up. Do you split the fingerstick specimen and send half of it off to the comparative method, or what have you envisioned doing with fingersticks? Or have you done anything with fingersticks before that would be helpful to us here?

DR. BECKER: Well, this is the first of the opportunities we have had to try to consider the hemologic aspect of fingerstick settings.

DR. BULL: You have no previous experience then with --

DR. BECKER: One kind of approach to look at that is that you have a patient, and I think it was on one of the slides as well, that the patient has a true value for the analyte. In the waived setting, the expectation is to use a fingerstick setting that the result from that might be compared back to what you consider to be at least as equally valid or result for a professional devices using venous blood, so that becomes --

DR. BULL: That would be acceptable in terms of your understanding of what you're after?

DR. BECKER: That certainly has been an expectation that we've pursued, yes.

DR. BULL: Thank you.

DR. BECKER: Now, I don't know whether that has been actually encountered, and I'd have to ask chemistry or one of the folks who have much more experience with having to do with waived for their comments concerning how well that has worked out in other settings.

DR. BULL: Thank you.

DR. ADCOCK: Dr. Kost, would you like to --

DR. KOST: So if I understood you correctly, the FDA has really not yet considered the difference in those two sample types per se in regard to what we're discussing today?

DR. GUTMAN: We've not considered it in this product line, but in chemistry, for example, if you look at glucose meters, it's quite routine to do fingersticks and compare to venous blood. So we have a lot of, we have a lot of experience comparing -- using as truth of the standard lab technique, and then the alternative being the fingerstick, but not so much in the context of the product that's being discussed today.

DR. KOST: One question for Dr. Becker. As the anxiety level and excitement both elevate today in this discussion --

DR. BECKER: Well, let's hope not.

DR. KOST: -- the FDA previously heretofore have a record in this particular area, for this question of considering outcome studies, have you done them? Has there been a demand or requirement for that?

DR. BECKER: Are you speaking about that in the waived setting or in the 510(k) setting as a whole?

DR. KOST: Anything specific to the issue today.

DR. BECKER: I'm not aware of anything with respect to the issue today dealing with hemologic testing that has been -- to need outcome studies for a decision.

DR. KOST: Thank you.

DR. BECKER: If I think of something a little later on, I'll try to interject that.

DR. ADCOCK: In an effort to move on, I would at this time to invite our guest speaker, Ms. Judy Yost, from the Centers for Medicare and Medicaid Systems, CMS, to approach the podium, but it looks like --

MS. YOST: Good morning, everyone. It's a distinct pleasure to be here and share this time with you. I apologize in advance. I heard here this

morning that the air quality was pretty poor. We're supposed to stay inside. So I guess that's kind of why you're here, but you'll also notice my allergies are overreacting.

When I first started in the laboratory field, back then only medical technologists performed the testing, and almost all of the testing was performed in a central laboratory on major pieces of equipment or manually. Before I really date myself, though, let's move onto the present where manufacturers have met or exceeded the bar and developed portable and/or bench top analyzers that are robust and a significant portion of testing is now being performed in point-of-care or ancillary testing sites. For example, if you look at CLIA enrollment data, over time you'll see that in the late '90s, three to four hundred pharmacies were performing testing. Now, it's over 3,000 pharmacies, and just multiply that by other types of sites where testing can be performed. You just need to use your imagination.

In any case, CMS strongly supports point-of-care testing because of the access and convenience for patient care, but we still maintain the responsibility overall to ensure that all testing is

accurate and reliable regardless of where it is performed. Because we believe and we have experienced that you can call a test a screening test or a diagnostic or whatever you want to, but we all know that medical decision-making is being made using that information.

In addition, the rest of CMS is also slowly moving and realizing that they should only pay for quality testing, but that's a subject for another day.

Thus, you'll see that my presentation focuses on the intent of CLIA, that is to ensure accurate and reliable testing.

You'll also see that the number of entities performing testing, with absolutely no oversight, represents 60 percent of the 203,000 laboratories enrolled in the CLIA program. CMS and its partners in laboratory oversight, including the approved accrediting organizations and the exempt states, the CLIAC which is the Advisory Committee for the CLIA program, have all expressed concern about the testing performed by less educated and trained individuals with no oversight.

My PowerPoint has an extensive list of questions and concerns for your consideration. These

are based on our experiences in the field. In the essence of time, I'll try to hit only the key points, but you'll have the entire list before you to review.

Just as a point of clarification, I believe it's been inferred in the discussion, but maybe not as clearly.

The CBC is currently considered a moderate complexity testing device. However, if abnormal cells are identified in a differential, that differential then defaults to high complexity. So there was some thought put behind this. I'd also like to thank Ann Snyder and Karen Dyer of my staff for developing the PowerPoint I'm using today.

So what I'd like to talk about is a little bit of background and data from our Certificate of Waiver Project, some of the concerns that CMS has about the waiver of a CBC and differential, and also provide you contact information. Again, as others have indicated, waive tests are simple laboratory examinations and procedures which employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible and pose no risk of harm to the patient if the test is performed incorrectly.

The only standard for Certificate of Waiver

laboratories, that is laboratories that perform only waived testing, is to follow the manufacturer's instructions. There is no PT required. There are no laboratory director qualifications and, of course, the laboratory must enroll with CLIA at CMS.

So regardless of where testing is performed, or the other types of testing performed in the laboratory, if there's a higher certificate, there is no oversight of waived tests.

As part of our Certificate of Waiver Project, each laboratory had to respond to questions about the testing that it performed.

Back in 1999, Colorado and Ohio took the initiative to visit a number of Certificate of Waiver laboratories. Then they discovered that 50 percent of them had some sort of a quality issue in their laboratory.

As a result of those findings, CMS expanded the pilot to eight additional states, that are listed here. In that pilot, we found that approximately 32 percent had quality problems. As a result of that, CMS went nationwide, and we are continuing since April of 2002 to visit two percent of the Certificate of Waiver laboratories each year.

These visits are actually considered

educational. We have no statutory or regulatory authority to actually survey these laboratories routinely. We are allowed to visit, to collect information, to respond to a complaint or to provide education if we wish, and that's the basis for this ongoing project. We cannot assess fees for these visits as well. So we are currently using excess funding to accomplish this project.

Let's move up to 2006, and here we can see that approximately 31 percent of the laboratories we visited were still not following the manufacturer's instructions. If you extrapolate that number, it comes out as 37,000 laboratories potentially are not even following the manufacturer's instructions. They may not even have them or may not have the current version.

Just to kind of put a perspective on this, when we first started surveying laboratories in the non-waived laboratories, back in 1992, we found that about 30 percent of previously unregulated laboratories were not performing any quality control or following the manufacturer's instructions. Our data today tells us that that number is at about 5 percent because of routine oversight and the education that we provide to those laboratories as

well. We feel that that remaining 5 percent is probably the result of new laboratories coming into the field as well as turnover in those laboratories or other significant changes.

One thing that's important to point out, however, is that when we revisit laboratories that initially had problems on that first visit, we have found that up to 85 percent of them have demonstrated improvement because of that educational intervention.

Unfortunately, due to funding and resource limitations of the CLIA program, because it is user fee funded, we cannot expand these visits at this particular time, but we can certainly demonstrate that that education is successful.

In addition to CMS' studies, CDC and the State of New York also did corresponding studies that were reported in 2004 at a CLIAC Committee meeting. Their findings included the fact that high staff turnover occurred in waived testing sites, and we continue to see that now. There is a lack of formal laboratory education, limited training of the individuals performing the testing. There is a lack of awareness concerning just basic good laboratory practice, how to collect and handle the specimen, how to accurately report results. Partial compliance

with manufacturer's quality control requirements was identified in 55 to 60 percent of those laboratories. So they do clearly correspond to CMS' findings.

So, of course, our question today is have Certificate of Waiver laboratories and test device performance improved sufficiently so that approval of a waived CBC test system will not be detrimental to patient care?

Since 1992, we talked about the eight tests that were listed in the regulations. We have about 100 analytes now that are waived, but this represents actually thousands of different manufacturers' test systems. The number of laboratories that have a Certificate of Waiver, again those that only do waived testing, has grown to 60 percent of the over 200,000 laboratories enrolled.

Here this is graphically represented. That certainly makes a striking picture, and I think here it's interesting to look at the transition of laboratories over time, based on the types of testing or certificates that they have under CLIA. You can see again this growth in the way laboratories, again they only perform waived tests. Of those 122,000 waived laboratory tests that are currently enrolled in CLIA, about 70,000 of them are physician office

laboratories. So those labs may have a physician available to help with the clinical interpretation of test results, but the remainder of those do not necessarily have a physician because there are no personnel requirements within CLIA. This data, by the way, is directly from the CMS CLIA data system, if you need a source.

If you look at the accreditation and compliance laboratories, those are the laboratories that do moderate and high complexity testing. Certificates are required for the highest level of testing in CLIA, thereby some of these laboratories may also be doing waived testing but only the non-waived standards, only apply to the non-waived testing. If a laboratory is performing waived tests under this scenario, it still is not subject to oversight. We can hope that there might be a little bit of an expansion, but we can't guarantee that because we cannot require it.

Waived testing again, I think several folks have said this, provides for a very timely, efficient and convenient patient care and, of course, provides good access to patient care as well. We could certainly see that it's continuing to increase, but the increased testing does come with issues and they

are the same issues that we iterated back with the CDC studies.

I've outlined the CMS concerns with regard to the CBC waiver at this time, pretty much how the regulations, the CLIA regulation flow which is similar to the path of workflow in the laboratory.

So I'll start with some general concerns and, of course, this is the question of the day. Should an automated CBC and differential be categorized as waived? Does it meet the definition of simple and accurate? How does the device perform under real laboratory conditions? We just heard about that, with actual testing personnel that have no training or education. And how are the varying hematological and patient populations addressed as well? What is the level of expertise necessary to operate the device and what level of judgment is necessary to interpret the test results? And, of course, is there any kind of data management capability for patient identification and to store and retrieve historical tests and QC results?

Moving onto pre-analytical for the instrument, patient identification is clearly an issue with us. I think all of you, you probably have to be under a rock if you're in laboratory medicine

not to know that this is currently the number one patient safety issue in this country, and many folks have undertaken numerous efforts to reduce those errors. On the plane back here this week, I read an article in Clinical Laboratory News of a study using some CAP information where a large number of laboratories voluntarily reported their error rates for patient ID, and they ranged from less than 1 percent in some laboratories to greater than 10 percent of their specimens.

In addition, some of the other concerns are about maintenance, how extensive is the maintenance required for a particular device? What happens if the maintenance isn't done? We actually experienced unfortunately with our Certificate of Waiver project the actual death of a patient in a nursing home because of a glucose device that was not maintained.

Moving onto the operator of the instrument, clearly training is an issue. If you have to train someone to perform the task, then is it truly simple. What type of setup is required? And can the setup features be locked? How does the operator apply the specimen to the device?

Specimen collection. We just heard a little bit about the fingersticks but also we have a

potential for heelsticks here, too, I would imagine, and we all know that that process with our laboratory background is very technique dependent and will directly impact the quality of the results.

What kind of flags and errors are available if there are collection problems such as those listed here? Is there any kind of specimen preparation required as well?

Clearly the analytic validity studies need to be very robust as well as the stress studies that FDA has been discussing today to include all of these specifications for the particular tests.

Under instrument validation, the other areas, clearly the clinical validation studies with regard to the disease states in hematology and the different types of patient populations that may be tested using this device has clearly, besides the general practitioner, that has a normal population, I think lot of specialists will be very interested in a very accurate and reliable CBC device. What kind of comparison, this was also brought up this morning, to analyzers with different methodologies have been done? Has it been compared to the industry standard? Is there proficiency testing data? Even though PT data uses a fixed sample, it still provides a good

outcome measure of a device performance. It is just helpful information in this very complex decision-making process.

With regard to reagents and quality control, under the analytic phase of testing, what are the test limitations? What are the types of precautions that the manufacturer has indicated in the package insert? And will these be flagged by the device? Is the package insert clearly written and concisely articulated? Is the test process time sensitive? What is the impact if the testing is delayed or the specimen sits? We believe that external quality control must be required at a minimum with each new lot or operator.

Are the manufacturer's quality control materials available? Are there any at all? Are they stored at the same temperature that the reagents for the device are stored? Are they in the same box? The easier you make it for the laboratory to use the QC, the better change you have of the laboratory performing that quality control.

For example, just as a bit of background, moderate complexity quality control requires two levels of QC each day of testing. It is also important, of course, to indicate what other

requirements are applicable.

In a testing scenario, where there are really no standards and no oversight routinely, quality control becomes very critical to ensuring test accuracy on a daily basis.

What types of internal quality control and calibration are present in the device? A built-in control, by that we mean either it's built into the device, it's internal and it's on board, or it's a procedural control.

Is the device factory calibrated so that if there's a problem with calibration, it can be returned to the manufacturer? Are there any flags in the system if the QC or the calibration are unacceptable?

What is the technology utilized to count the blood cells? For example, impedance. Are all types of white blood cells identified or are only certain types? Is the variability of cell sizes addressed by the device? Because we all know in certain disease states, you will find that even the standardized cell sizes will vary in those cases. Are interfering substances identified? What about abnormal cells? Are they correctly identified? Are they flagged?

Continuing under patient testing under analytical, are there fail-safes or lockouts for fatal errors? Does the software prevent result reporting? Can error codes be overridden by the operator? Must the test performance be supervised? In those situations, obviously a test could never be waived. Are there numerous steps in the testing process and how complex are they?

Let's move onto post-analytical, the reports resulting phase of testing. Normal versus abnormal types of tests. Again, are there error codes that are flagged and included on the test report? Does the manufacturer provide reference ranges for the various types of clinical or patient populations?

In summary, I'd like to highlight some of the key concerns that again based on our experiences in the field with laboratories, and particularly waived laboratories, we have a rhetorical question for you.

Should an automated CBC and differential be categorized as waived?

Does it necessarily meet the definition of simple and accurate?

What is the level of expertise to operate

the device and the judgment required in order to interpret the testing results?

How does the device perform under real laboratory conditions using the actual testing personnel with no training?

How are varying disease states and patient populations addressed in the result reporting and the analysis?

Is there no risk of harm if these are performed incorrectly?

We have seen issues throughout the entire testing process from pre-analytic to post-analytic and have concerns about the fact that there is no data management capability potentially in these devices as well.

And so based on these multiple concerns with this type of a test system, we believe right now that there are still significant enough potential areas of risk that must be addressed to reduce the likelihood of harm to the patient.

I've also provided you some contact information. I want to thank you very much for your time and attention. I know it's lunchtime. Our challenge at CMS is always a balance. We have to ensure accurate and reliable testing, but we also are

obligated to ensure that access is available where it's needed.

So we challenge you to, with that same though, and we hope that we've provided you some additional ideas to consider. Thank you very much.

DR. ADCOCK: Does anyone on the Panel have a question for Ms. Yost?

DR. KULESZA: Yes. Ms. Yost, you say -- I have the document here, which I think you used for some of the basis of your presentation. The lab does not have current manufacturer's instructions, 32 percent overall; does not follow manufacturer's instructions, 16 percent. I would like to dig deeper into this and ascertain what does this really mean in practice? I don't follow manufacturer's instructions when I drive my car. I'm fairly successful at driving. So is this indicative of the real life consequence in a patient setting, i.e., are we making medical errors or are these devices presumably so simple that not following the instructions isn't that much of a problem? I mean, what is your -- can you from the limited -- I understand that you had a limited study, but is there any insight that you could provide?

MS. YOST: We do not have any outcomes

data. I wish that we did, but we do not unfortunately. What we have evaluated is the one requirement that we have under CLIA, which is to follow the manufacturer's instructions for test performance and other ideas considered in that package insert.

Our finding is that we believe that this, in total, provides a high potential of a risk of an erroneous result, which ultimately could cause harm to a patient if we have tests that are used to make treatment decisions. Many of the waived tests currently are used directly. We even know of glucose tolerances being done on waived devices where decisions are being made. The hemoglobin and hematocrit are clearly going to lead to a clinical decision. The prothrombin time that is waived again will also. A number of the chemistry tests that are also waived will also cause a clinical decision. So it is within our professional judgment in reviewing those laboratories that we compiled this information to make you, the public, and whoever needs to be aware of the concerns about that potential risk of harm based on our findings.

DR. ADCOCK: Dr. Kost.

DR. KOST: Do you close any of these labs

when your surveys are rather adverse?

MS. YOST: We have.

DR. KOST: What percentage have you actually closed?

MS. YOST: Very little because actually, believe it or not, most of them are happy that we come because no one else talks to them, you know. They get sold the device and then never to be seen again. So they're actually happy. We actually provide basic laboratory practice guidance to the laboratory. We actually leave a document in the laboratory that lists some key ideas about how to handle the specimen, how to collect it safely and correctly and so forth. And as a result of that, we find that, like I said, I think you saw, my data shows that at least for those that we have revisited, that we only go back to the ones where we see serious problems because again it's a resource issue.

So you kind of have to pick the hanging fruit of the worst ones on the top of the list. We go back to those, and we do visit those and check to see whether they're following anything because, you know, there is the chance you walk out the door and they're back to their old same, you know, whatever they were doing before, but again at least 70

percent, up to 85 percent of them are actually following a lot of the stuff we've provided. They want to do a good job. They just don't have the wherewithal because they're not laboratorians. They don't have the education. They don't have the training because there are no requirements for such.

We have, however, had a couple where we actually had immediate jeopardy to patient health and safety, in response to your question, where we have pretty much given them notice that if they do not correct everything, we will close them down. In most cases again, they usually respond and they correct their problems. But if we have to, we will remove a certificate. I don't have exact numbers with me unfortunately, but we have done that, and we will do that. I mean, that's the guidance that we provide our surveyors with this project because it's not enough to just say, okay, you have a problem. We have to do something. That's our obligation as regulators is to make sure that we guarantee the safety of that testing.

DR. KOST: Does anything go to the manufacturer in such case you might put somebody on "probation" or --

MS. YOST: No, because again -- sometimes

we get manufacturers who contact us because of what we may have found, but in most cases, a lot of it is the test performance, and maybe it's based on handling issues. We don't necessarily have -- we haven't really identified a huge number of device problems, but we're not looking necessarily at that. We're really looking at what the lab is actually doing because that's CMS' role. FDA, you know, oversees manufacturers. So we kind of have it divided up. Obviously, if we would see something, we would clearly report it. We do have mechanisms to accomplish that.

DR. ADCOCK: Dr. Wang.

DR. WANG: First of all, I would like to know if I can ask reimbursement question?

DR. YOST: No.

DR. WANG: No, I cannot.

DR. YOST: I can't answer them, sorry. I'm CLIA. I don't want to answer them anyway, not these days.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: Yes. I was surprised to hear you and I think an earlier speaker also mention that a substantial proportion of the laboratories that are waived laboratories, there's no physician on

site. And since the purpose of point-of-care testing is to get the results to the physician faster, I'm puzzled as to what these labs are if there's no physician on site to receive the results.

MS. YOST: It's a matter of access. So you'll see in say a remote area, in like a rural health clinic or a community clinic, you'll see testing being -- anybody can perform a waived test, and even us. And so there's no requirement that there be a physician present, but one would assume that somewhere along the line there was a healthcare provider that ordered that particular test and will ultimately receive it if there's a problem. But at this point, it's really to provide that access. So again, it is not strictly physician -- don't be deluded that it's always a physician office lab because it's not. I mean, there are the better proportion, but there are a whole lot. 50,000 is a lot of labs that don't have a doctor necessarily there. And most of those don't.

You know, even on an ambulance, on the way to the hospital, they're doing waived testing, too.

DR. ADCOCK: Dr. Bull.

DR. BULL: I want to pursue this question just a little bit further because we're sort of being

asked to make decisions with an environment that's stipulated that the operator of these devices will have essentially no training, no knowledge, and maybe no education. And this may be outside the limits of what we're allowed to question, but I know in my state, a person who draws a blood sample has to have a minimum degree of training, and I think even people that put cosmetics onto other people's faces have to have some sort of training. And why is it that we have gone down the road of allowing people to waived testing with no training, no education, and maybe no talent?

MS. YOST: Ask your Congressman. We didn't write them. We just implement them. We do our best under the circumstances to make it work.

DR. BULL: Well, the reason that I ask that is that with -- it would make our job a lot easier in terms of specifying what the machine should do if we had some person with a reasonable IQ and a couple of weeks of training as to what is blood and, you know, what's urine and the difference between them and things like that.

MS. YOST: Right. Yeah. We hardily agree.

DR. BULL: Thank you.

DR. ADCOCK: Does the Panel have any

additional questions at this time? Yes, Dr. Kost.

DR. KOST: I have a question for the FDA personnel here. Maybe it's not fair game. Should I let it go until after lunch?

DR. ADCOCK: Perhaps one question.

DR. KOST: Okay. I'm not so sure about whether we're between a rock and a hard place on the issue at hand today. Let me give you a what-if. Suppose a manufacturer has a point-of-care device that's already made it through 510(k). Can they then use that as a predicate device for the waiver application in this specific case?

DR. GUTMAN: No, they can't.

DR. KOST: For what reason cannot?

DR. GUTMAN: Because the 510(k) program is based on a statutory requirement to show equivalence. So you show one device to another. The reason that our statisticians went through the traceability trail is that the CLIA actually requires that the assay be accurate. You can't be accurate just compared to anything. You have to be accurate compared either to a -- actually at the time that the program was first implemented, you had to actually have either reference material or method or you couldn't be waived, and the idea of introducing traceability to

allow things to go to some higher order that might not be a recognized reference material or method came from AdvaMed, and it went to the CLIAC, and it was discussed at a subcommittee of the CLIAC. So it represents actually somewhat of a liberalization in the accuracy base but the only way you could use the predicate as the basis for determining performance, if the predicate was considered reference method.

DR. KOST: Well, is the corollary then that we as a Panel or I as a person could recommend that the accuracy be proven per se?

DR. GUTMAN: Well, we would argue that that's the core of the question that we're asking you.

DR. KOST: Okay. Thank you.

DR. GUTMAN: It's not a matter of accuracy. It's a matter of, you know, what do you mean by has been met?

DR. ADCOCK: Thank you. We will now break for lunch. We will reconvene again in this room approximately one hour from now, at 1:15. Please take any personal belongings with you at this time. The ballroom will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene. Thank you.

(Whereupon, at 12:05 p.m., a luncheon recess was taken.)

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

(1:22 p.m.)

DR. ADCOCK: At this point of the meeting, we will focus our discussion on the FDA questions. Copies of the questions are in your folder. Ms. Bautista will read the questions, and at this time, I would like her to show the first question.

Oh, pardon me. I apologize. Prior to having the discussions, we've got about a 15-minute period where we would like to move onto a general Panel discussion, and then at that time we will move on to the FDA questions.

It's at this time that we can ask additional questions of the FDA, and we can also have a discussion amongst ourselves.

I know that I have a question, and it has to do with the flex studies, the studies to determine the problems that can occur with the instrument. Who drafts these studies and are there requirements that certain areas of possible interference or complication be looked at?

DR. GUTMAN: If you look at the guidance that was provided, the guidance on flex studies actually has 17 examples of possible issues to be looked at. It's the company's responsibility to do

what Ms. Benson suggested, is a risk analysis of everything that is likely to go wrong, and then they're supposed to demonstrate what fixes that, you know, ideally if something goes wrong, there will be no report generated or, you know, there will be a lockout feature or something that the report will say something went wrong rather than. That's our first choice is to make it fail-safe or failure alert. Sometimes there are other ways to mitigate. The weakest way to mitigate is through labeling. Labeling sometimes is not read but it's job then to quality control those when we do the reviews, so to look and see if we think that, in fact, all of the right questions have been asked and the risk analysis is complete and the answers sound good. And so it's a shared responsibility. The manufacturers actually initiate that, and it's worth pointing out that the risk analysis that we're performing for waiver actually isn't fundamentally new. There's supposed to, under their quality system regs, be doing that kind of risk analysis anyway. It's just that in the context of the 510(k) program we don't review that.

DR. ADCOCK: Can you repeat that last point again for me, the difference.

DR. GUTMAN: The risk analysis that we're

asking for in the waiver program is actually something that they're required to do under the good manufacturing practices in the design of the product. So it's not a fundamentally new waiver specific. It may be a little bit more intense in the context of waiver, but it's an extension of the way they're supposed to design and make and test their product for commercialization.

DR. ADCOCK: Dr. Wang.

DR. WANG: Is there a minimum number of samples you need to do for each possible flex study? Like each stress situation.

DR. GUTMAN: No, we haven't set any particular number.

DR. WANG: So they could just do one?

DR. GUTMAN: I doubt they'd get away with one.

DR. ADCOCK: Dr. Kulesza.

DR. GUTMAN: We ask for at least two.

DR. KULESZA: Yes, I have a question for Ms. Benson and Dr. Becker. So we're talking about equipment that will be, if this comes to pass, would be waived, i.e., will not have any supervisory capability should something go wrong. Most likely this instrument will have to operate very

independently, very reliably. Aircraft people, I don't know this, but I read about it, test what's called test to failure. Your 360 samples is I would imagine rather inadequate to test a machine that is supposed to perform independently and reliably over a six month period without really major maintenance or major ability to perform checks upon its quality control. Have you given any thought to the process of testing to failure, i.e., if the machine is expected in its lifetime to perform CBCs, is it going to break at number 500? And is there any thought given to that process being a little bit more robust than just two weeks in a particular setting to test for other aspects of possible failures?

MS. BENSON: Okay. I think that when devices are presented for waiver, they've also been through the 510(k) process. So they have been tested generally in that setting as well. I don't think we have a requirement that they test to failure, but that's the idea of the flex studies is to try to stress the system and make it fail as far as those items that we've listed in the guidance. I don't think we make them test, you know, how many tests they would actually do before the whole system fails.

DR. KULESZA: But I would imagine that that

would be something that would be worthwhile to look at, not only from the standpoint of 360 samples may not be adequately reflective of all the clinical scenarios that a waived system should undergo, but is that something that you would actually not be -- like how many tests is enough and how many cartridges does it take to wear out the groove in the door, a simple question of that nature.

MS. BENSON: Well, I think during the manufacturing of the device, they would know -- they would do testing that would predict I think where the device would fail. Obviously no manufacturer wants to produce a device that's going to fail in the, you know, in the marketplace. So they would not want to have a device that fails. So I would think that in developing the tests as Dr. Gutman talked about, the type of risk analysis, they would be doing that as part of good manufacturing practices, so that they would know some information about the device.

DR. GUTMAN: But to speak to your point, we actually have not in the context of developing, you know, at CDC when they develop guidance, when we develop guidance, that idea was never introduced as concept to testing to failure and we certainly never contemplated, maybe an error, but we've never

contemplated testing literally perhaps thousands or tens of thousands of samples in order to test failure. So that's intellectually a concept that's not been on the table before.

DR. KULESZA: Because it's really easily addressed in the clinical lab because contracts are such that within an hour, red shows up. I would imagine that that would not be possible for a waived instrument should it be if similar failure capability.

DR. ADCOCK: Would you like to respond to Dr. Kulesza?

DR. AZIZ: Yeah. They can provide the service I mean, but the question is really is the personnel doing the testing, and I really feel like, you know, with the situation that we have in hand, we really need to look at the users. Somehow we're saying like, you know, we need to see three sites with three different users in every site. That is not representative of the real life where these instruments are going to be. I don't think so. You know, usually if we're talking about the physician office labs, the turnaround in personnel is just amazing, you know. So you will have people that work for a day or two, and then they move on and they move

on and they move on. And, basically, usually you're trying on the stop. This is how you run this test. So I really feel like, you know, we need to put a huge emphasis on the personnel.

Most instruments in the clinical lab these days are simple to operate, even in moderate complexity, you know. Even the huge hematology CBC analyzers, basically you just introduce the sample to them and they will do all the testing. It's the interpretation that we are really worried about, and this is where we really need to focus our efforts. And it goes back to the users, and as we heard from so many speakers today that, you know, some of these people, they will have no training whatsoever. Most of these places, they will come in and install an instrument, train you in an hour, and that's it, you know. And then there's no annual competency. There's no regular competency. There's no quality control requirement that needs to be done on a regular basis. I think that's where we really need to put a lot of effort in producing the most capable person to run this test, especially if there's no physician around to interpret this result.

You know, the fact that the test is simple, I really think the huge LH analyzer that was

mentioned earlier today, it's very simple. It's very quick. So that's not comparing nothing to nothing. I mean in my opinion, that is not the issue, okay. It's the interpretation. I'm going to stress on that again and again. It's like the interpretation of these results, the flags and how we interpret that. So somehow I would like to say like, you know, where the sponsors will train, will offer training, ongoing training, there must be competency checks, ongoing competency checks on these users that are doing the testing.

DR. ADCOCK: Dr. Norback.

DR. NORBACK: With regard to the flex tests, I had raised the point earlier that I would hope that this would be a time that we could challenge the instrument to make sure that it did not produce errors that were beyond limits that would be dangerous for patient care. And so, in addition to some physical conditions that could cause breakdown of the instrument or just erroneous results, I would like to challenge it with the samples that we know are going to be difficult to analyze, like samples that are hemolyzed or high levels of bilirubin or lipidemia or short sampling or partial clotting, and cold agglutinins and rouleaux and osmotic

abnormalities and platelet agglutination and giant platelets and unlysed erythrocytes and nucleated red cells and megakaryocytes and red cell inclusions, cryoproteins, mucin, leukocytosis, hemolysis, microcytosis, blasts, abnormal lymphocytes, and so then we would want to really challenge it to make sure that blasts are not called lymphocytes or monocytes, and this would also be a time I think that we could challenge it with very low levels like what type of a reading will we get with the clinical sample that has a platelet count of 10,000. I guess, in my estimation, 30,000 would not be an acceptable answer, and so we could identify values that if they're very low, there would have to be a certain level of accuracy, and if it was beyond that, that would be clinically significant and perhaps very dangerous to the patient, and then for some values, high values are important. High values of platelets would be important, and so I'm just hoping that we have the opportunity to create a list that the instrument can demonstrate its capabilities on, not so much in the clinical period where the routine samples are looked at, but when it's definitely challenged with samples, that we want to know if it can give us the appropriate answer.

DR. ADCOCK: Dr. Bull.

DR. BULL: It occurs to me as we're talking about the way of challenging the instrument that Dr. Norback has talked about, that all of us here are familiar enough with the processes in the clinical laboratory to have overlooked one of the most obvious and glaring errors, talking with my fellow panel member here to my right, she points out that if you put a receptionist in charge of this instrument, it's unlikely that she'll bother to invert the specimen before she presents it to the instrument, and depending on how long it's been sitting, you could get any value from very severe anemia to actual pure plasma if you let the specimen sit for any reasonable length of time and there's a high sed rate.

Given that we have been tasked by the FDA to have those sorts of things not affect the accuracy of the results, are these instruments going to take the specimen and mix it four or five times as every good laboratorian would before they even analyze it, or are we going to have to contend with the possibility that somebody will actually take a plasma sample and stick it under the instrument?

DR. GUTMAN: Well, you get to recommend.

DR. ADCOCK: Ms. Rice.

MS. RICE: What he just talked about I ran into a site I surveyed. I walked in and the receptionist was running the samples and did not know to invert them. We can have all of these tests on instruments to make sure they operate at every level, but it still comes down to the person looking at the results, and if they're untrained, they won't know if it's an incorrect result or not.

And training is what is required for this. The only difference in personnel standards being waived and moderate complexity is training. If you're going to train them, leave it in moderate complexity where you have the oversight of being inspected, QC, proficiency testing, and make sure that everything is covered, you have all your bases covered and you will recognize the erroneous results.

MR. BRACCO: Can I just make a comment to that?

MS. RICE: Uh-huh.

MR. BRACCO: I think we need to be careful that simple doesn't mean you don't need to be trained. I mean, if it's a simple test, you still need to know how to unpack that dipstick or whatever you're using. So the receptionist that we speak about, if that person is trained to invert the sample

before it's used, I guess the question has to be, can a layperson understand those instructions and apply them consistently?

MS. RICE: Can I address that please?

DR. ADCOCK: Yes, Ms. Rice.

MS. RICE: In Georgia, we're getting away from RNs in physician offices. We're going to medical assistants. There's high turnover. You won't find directions for the waived testing. If you do, you're lucky. They may not be current. It's one medical assistant telling the next one how to run it. You lose a lot in the detail. They have 10 other things they're doing. They aren't only running lab tests. All they're interested in is producing a result. They don't have any idea if it's correct, if it's compatible with life.

DR. ADCOCK: I'll take one last comment from Dr. Ng.

DR. NG: I want to get back to Dr. Aziz's comment. I want to just state at a very high global level, I don't understand the role of a device that provides only a total WBC, a total red count, and maybe a platelet count and maybe a three or five part diff. I say that because when somebody comes to me with a hemoglobin issue, my first question is what's

the red count, what's the MCV, and what's the RDW? If I don't have that information, I cannot interpret the hemoglobin.

Secondly, with the white count discussion I heard this morning, there was a discussion about pediatricians using it to treat otitis media with or without antibiotics. There was a related discussion about the emergence of drug resistant organisms by over prescribing of antibiotics. To me there are two issues buried in there. One, if you use a single threshold white count over which an elevation would predicate antibiotic treatment, you're missing the temporal course of a bad bacterial infection, right. When you get infected, the white count goes up, but as you turn the corner and you get really bad sick, the white count goes down. So what are we going to miss at the false negative end, and what are we not going to treat that could have a bad outcome that we could have avoided. So I'm worried about that.

I'm worried about people using the emergence of antibiotic resistance as an indicator for this kind of test. In the pediatric population, how many articles have been written about the unnecessary prescribing of antibiotics for various clinical conditions. There certainly is a wealth of

evidence out there based on whatever the clinical presentation is, what is the pre-test probability, it's viral versus bacterial, and based on that, that alone is probably better than any test to tell you what you need to do.

My final comment about having a waived CBC device is a CBC is not a diagnostic test in most cases. In most cases, it's a screening test, and it can point you to one of probably 100 different diseases. How are we going to have these easy to use devices now boxing people into different diagnostic categories that are probably going to be inaccurate because they only have a piece of the peripheral blood picture and not enough to arrive at the correct diagnosis. To me, that spells unnecessary testing, inaccurate diagnoses, and patient harm.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: Thank you. I'm glad that you brought up the question of clinical indications because the only indication that we heard about this morning was a decision whether or not to treat with antibiotics for an elevated white count, and I think that we really do need to consider other clinical indications and how the test results might be used, particularly in an outpatient setting where I think a

waived CBC would most likely be used. And some of those indications might include decisions, whether or not to give patients chemotherapy based on a minimum white blood cell count, or it might be a decision whether or not to transfuse a patient with red blood cells based upon a hemoglobin, hematocrit result, or transfer them with platelets or, for example, to do a bone marrow examination, an invasive procedure based on a low platelet count. So these are some of the other clinical indications and decisions that might be considered based on this hypothetically waived test that I think also we need to consider the questions that are posed to the panel in the light of those types of clinical indications.

DR. ADCOCK: Thank you so much. At this time, I think we should probably move to the questions, and we'll focus our discussion now on the FDA questions which are in the folder, and Ms. Bautista will read the questions at this time.

MS. BAUTISTA: Okay. Question Number 1, Pre-analytical. In performance CBC/Diff tests, laboratory professional traditionally control for a variety of pre-analytical variables such as hemolysis, gross presence of interfering substances, such as bilirubin and lipid, short or long sampling,

or partial clotting, such as fibrin strands.

Considering question 1, considering the pre-analytical issues, can CBC/Diff testing meet the waiver criteria that the test is simple and shall have an insignificant risk of erroneous results?

If the answer to the question is yes, (a) should submissions address pre-analytical errors specifically in the waived setting? If so, how? (b), please identify any pre-analytical sources of error for CBC/Diff that will be particularly difficult to control and how they might be addressed.

If the answer is no, please explain why.

DR. ADCOCK: Dr. Bull, would you like to begin the discussion?

DR. BULL: Do you want yes or no answers to these from each of the Panel members?

DR. ADCOCK: Certainly.

DR. BULL: Well, I don't think there's any possibility that the test can be described as simple and having an insignificant risk of an erroneous result. So in answer to number one, I would have to say CBC/Diff testing is not simple, and there is a very significant risk of an erroneous result.

DR. ADCOCK: Can you provide any explanation, any --

DR. BULL: Well, we've had a list of all of the possible things that are taken in consideration in a well-run laboratory when the test is being done by trained personnel, but I'll go back to the question that Ms. Rice brought up and that is the very simplest requirement is that a blood sample be well mixed before it be analyzed, and it's not at all clear to me that it's possible to ensure that personnel who may have been introduced to the machine five minutes because the person who was trained didn't show up for work, I don't see how given the personnel standards that you can prevent somebody from analyzing the sample that nobody who's had any connection with the laboratory would even consider analyzing.

Now, having said that, it seems to me that one of the things that maybe we can do that's useful is say that some of these questions might be answered differently if there was some way of guaranteeing certain minimum standards of training on the part of the people who are going to use these machines but if we're forced to answer these questions with no training at all, and maybe only 10 minutes of experience with the machine, then I think the answer has got to be that it's not simple and that there is

a very significant risk of an erroneous result.

DR. ADCOCK: Do we have other Panel members at this time that would like to weigh in on this question? Dr. Sandhaus.

DR. SANDHAUS: Thank you. Well, my answer to the question is also no. The main pre-analytical error that I would like to address is partial clotting of the sample. Clotting may occur due to improper sample collection or mixing of the sample with the anti-coagulant. Clots are not generally visible by simple inspection of the tube. Ensuring proper mixing of the sample at the time of collection can reduce clotted samples but does not eliminate them completely.

Before the advent of automated samplers with the automated hematology analyzers, CBC tubes were routinely uncapped, and each sample was checked for clots by inserting a stick. With automated CBC sampling, the analyzer may produce a flag that suggests the possibility of a clotted sample, and then these are subsequently examined manually for clots in the laboratory.

But another clue to the possibility of a partially clotted sample is a platelet count that is unexpectedly low. Many labs have procedures that

require the technologist to check the tube for clots when a first time or unexpected low platelet count is obtained. Most labs also have rules for canceling CBC results if a clot is detected in the sample. Checking each tube for clots does not appear to meet the criteria for waived testing. It's difficult to imagine how this pre-analytical source of error could be eliminated in the waived setting because it has not been eliminated yet in the laboratory setting.

DR. ADCOCK: Dr. Wang.

DR. WANG: I have to say that before I got this assignment, I knew nothing about CBC. In order to render an opinion, I actually went to the hematology lab at -- and so I am willing to accept correction because maybe my observations were limited, but based on my observation, for automated CBC, according to my observation and what information I received, there's no prerequisite like checking for clot or rotate. Actually the machine does rotate the specimen, believe it or not, it does and at least the machine I observed, once the tube goes into the machine, the first step is to rotate the tube. And I don't know if that's sufficient or not.

So I do agree there are a number of pre-analytical issues that can generate inaccurate

results or spurious results that cannot be interpreted, but as far as the operation though is concerned, it seems that it's pretty automated, but my concern is how do you interpret the abnormal results.

So based on my observation, the specimen basically goes through the machine and the results are generated. If there's not flag, the results are issued. So it's already pretty automated or pretty waived.

The question is when there is a flag, what do you do? That's where we need intervention from trained personnel.

So I'm more concerned with the 30 percent that Dr. Becker presented this morning that based on two studies, approximately 30 to 35 percent of the specimens are flagged. That's when the intervention needs to take place. So if we can have equipment that simply in this case flag it and give a result, is just locked out and do not give any results, and that may be what's considering because it won't generate a result when the abnormal results generated because of hyperlipidemia or bilirubinemia, whatever, or clotting, partial clotting, like very abnormal low platelet count. So instead of giving the result, if

the machine just say fail out and say no result and it kind of force the personnel to take the next step and submit another sample to a central lab.

DR. ADCOCK: Dr. Ng.

DR. NG: Much of the discussion is focusing around blood collected in tubes. I want to address the possibility that blood obtained by fingerstick might be something to use. One comment of the things I see is point of care that interfere with accurate fingerstick blood testing.

Number one, people don't wipe the alcohol off, and it hemolyzes all the blood that comes out. So if you're measuring red cells, that could be a major issue to deal with.

Secondly, I am not aware, but I don't follow this literature that carefully, I'm not aware of the relationship of capillary blood counts relevant to venous blood. We certainly know glucose, there's a huge, here's a significant difference between arterial capillary and venous. So I'd be curious how those reference ranges would then be developed.

And then the final comment I want to make, one of the slides that made me sit up was on the one where it was postulated, maybe heelsticks might be

included in this. Heelsticks make me very, very nervous because those are typically done on neonats, and neonatal blood is the number one blood that flags out every time on my instruments because of all the nucleated red cells. So that's number one, and number two, what the heck happens to platelets in either fingersticks or heelsticks because you're just macerating it like crazy, and you would think that would generate, I don't know, generate a lot of thromboplastin, create platelet plugs, and then how accurate would be that fingerstick value. Those are just my thoughts.

DR. SANDHAUS: I have some follow-up on that.

DR. KULESZA: In listening to all of this, and all of these considerations are really dependent on the particular technology that is employed, so reading this sentence, considering the pre-analytical issues, can CBC meet, can it meet the test that's simple and have an insignificant risk of erroneous results, it all depends on the machine and the specifics of the technology that's under study, because presumably we can engineer out, if we put the spectrophotometer in there that checks for bili and checks for hemolysis, then we can addressed nucleated

RBCs and we can flag the machine. So it's a technical answer rather than an answer of principle here.

I don't know how to answer this question without having the constraints of the machine already explained.

DR. NG: If I could rebut that comment. In my CBC analyzers today, nucleated reds pop up in the lymphocyte and overlap with the lymphocytes. I don't care how good either your impedance or your spectro or your optical or your radial waves are, those cells overlap by size and some of their absorbance or reflectance characteristics. It is not 100 percent separation. Back to the WBC differential issue, I rely heavily on those scatterplots. Are those populations discrete? Then I can make a decision. If not, they're overlapping and the machine's wrong. Okay. I'm sorry I'm yelling, but when you don't have that picture in front of you, you know, you just have a total count and you have what you think it is, what's your recourse, and you don't know what's wrong.

DR. KULESZA: Right. So in that setting, what I would do is that would come out in the clinical trial because I reviewed like -- I went to

hematology lab, and I sat there looking at the scatterplots, the optical and impedance measurements, and the machine would flag iffy results.

MR. BRACCO: It's becoming clear that I think these submissions are going to be heavily weighted on these flex studies. As a matter of fact, it looks like the 360 study is really just a quick confirmation study, but these flex/robustness studies really are going to be the crux of those submissions, and there's going to be a lot of them. There will be a lot of them to answer all these concerns. The question is what would be the sample size and what's sufficient? You can't do 360 for every single one of them, but certainly these flex studies are going to be of high importance in that submission.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: Thanks. I wanted to add some information to the fingerstick and heelstick discussion because I think if fingerstick samples are going to be an option for this type of analyzer, that is important to discuss. And we did a study in our hospital to see if we could determine a benchmark for clotted heelstick samples on neonats because this is an issue at our hospital, and we determined that in our institution, that 6 percent clotted samples was

the best benchmark we could establish on neonats for CBC testing.

Now, that 6 percent benchmark for neonats was using experienced phlebotomists collecting the samples, and I think we have to be careful about extrapolating what's a benchmark for neonats to fingersticks for adults. They might be different, but nevertheless it suggests that there's a substantial rate of clotted samples when you use a capillary sample.

DR. ADCOCK: Dr. Kost.

DR. KOST: My answer is yes and no, predicated on the fact as pointed out that the instrument technically and theoretically, maybe futuristically, could evaluate the same suitability. However, personally I think it should be assessed in the actual setting of use, which is very challenging. But I wanted to read in the record a paper published by Barnes, P. W. Barnes, et al., called "The International Consensus Group for Hematology Review, Suggested Criteria for Action Following Automated CBC and WBC Differential Analysis," published in Laboratory Hematology, 2005, Volume 11, pages 83-90, because in this attempt to arrive at a consensus on rules for flagging and accepting what an automated

analyzer should do, there are several, and there's a bit of evidence-based study in here.

So, for example, every neonat in this set of rules is recommended for smear review. So it would seem that either the FDA would have to exclude some of these patient age groups and populations up front and/or work with the software and so on of the instrument to allow measurements to be performed correctly.

DR. ADCOCK: Dr. Aziz.

DR. AZIZ: Let me just give a quick inside from a technical point of view. The current analyzers in the market right now in moderate complexity labs, they vary between three part diff that you just really have to remove the top and expose the specimen. Not all of them makes the specimen. Those are the top ones, okay. But for the most part, for the small labs, physician office labs, you have to mix them yourself and you have to introduce the specimen yourself.

For safety issues, you, I mean you will go, if you have the money, the resources, you will go with one that is automated.

So I mean it's really -- it's just like comparing cars. You have something that is very

standard, something, very, very automatic with GPS and all that. So it's really not no comparison between analyzers. So I'm assuming for this to be a waived test or to be a waived instrument, analyzer, it's going to be very, very simple, very, very basic, you know, and most likely it's going to be a fingerstick, most likely.

So having all of that in mind, I mean we just also have to think about the current ones in the market because they might mimic something that is in the market already.

When we calibrating the instrument, we calibrate it with known reagents that we get from the manufacturer. Usually they're done on one mode or another, closed sample or open sample. So if you do it closed sample, you have to apply your calibration to the open sample, and I'm sorry if this is boring somebody, but, you know, it seems like, you know, some people, not everybody in this room, they understand the technical part of it.

So that concept is already here in moderate complexity instruments, and other things like, you know, it's always aggravated me, like we don't call them machines. We call them instruments or analyzers. Machines, you find them, you know, in

mechanic shops.

So these analyzers, you calibrate them to one method, and then you apply the calibration to the other method, whether it's open sample or not, and that's what we use for fingersticks. So I just want to clarify this to the Panel.

DR. ADCOCK: Dr. Norback.

DR. NORBACK: To answer the question, the instruments as we use them now are not simple, and we can get erroneous results that could affect patient care, but I also took the position that if the manufacturer can develop an instrument that recognizes all of the problems and lists every problem that we add to the list, and then either correct the problem like inverting the tube before it's sampled, or just identifying that we've got a clot and the result should not be used, and then states that, that results are not usable, then I think that conceivably, hypothetically it could be used in a waived setting.

DR. ADCOCK: Any further discussion before we summarize?

(No response.)

DR. ADCOCK: All right. This is difficult to summarize, but in general, and correct me, Panel,

if I've not captured everybody's thoughts, the Panel generally believes that CBC testing as it is currently performed with known instrumentation is not simple, and there is the potential for erroneous results. This may change should there be instrumentation developed that can properly identify the pre-analytical variables that we are concerned about and should an instrument be able to demonstrate such in an effective manner, then the panel generally believes that waived testing may be applicable to such instrumentation.

DR. KOST: Well, fair enough. She's looking at me. So I don't know what I said, but basically the paper that I cited is actually the underpinnings of what we do for flagging results for review in our laboratory. We've augmented it and tweaked it and what have you, and actually the list for flagging is qualitative, it's quantitative, it's operator based in some cases, and it's a long list. And I didn't see anything from in the packet I received from the FDA that properly addresses the long list of things that need to be done. So maybe I could add to it that this needs to be considered at a very fundamental level, and I would recommend that it be inclusive in regard to what a manufacturer would

have to demonstrate.

DR. ADCOCK: Dr. Bull.

DR. BULL: I would agree with your assessment that the present machines, and by the way, I didn't go to the hematology laboratory to find out how they worked because I had a hand in designing most of them. The present situation is such that I think we've got to answer the question no, but should a machine come along that addresses all of these things, I still think it's going to be impossible to have those machines operate safely in the laboratory if we are not allowed to impose some sort of training requirements on people performing this particular waived test.

Now, I understand how waived tests came to us. They came to us originally with very simple things like putting one drop or putting a dipstick in and then comparing it with a color but what has happened to us is that the requirements that these tests be so simple that no training is required for them, has now come back to bite us, and although it is theoretically possible to design a machine that would be complex enough to eliminate all these sources of error, on the machine basis itself, it would be so expensive that I doubt that we'll ever