see such a machine. I think the only chance that we have of ever getting machines into a waived status, into the kind of laboratories that we've been talking about today, is if we're allowed to impose some sort of training requirements, even if they're fairly minimal, on the people who are going to operate these. If we have to make the decision on the basis of a receptionist with five minutes of instruction being able to produce accurate and non-threatening to patient care results, I don't think that the manufacturers are going to want to put that kind of fail-safe device on a machine for a waived setup. It's just going to be way too expensive.

DR. ADCOCK: Dr. Ng.

DR. NG: I just want to comment. The article that Dr. Kost is referring to, we call in our lab, the 43 rules. Okay. So there are 43 rules in there, and they're predicated on was it 15,000 samples analyzed in 3 to 6 laboratories. It's a huge number of samples, and that those 43 rules were the only 43 that group could agree on, that there were a bunch of --

DR. KOST: 13,298.

DR. NG: Okay. 13,000, I was close, 200, okay, but there a bunch of more things that each

group wanted, but nobody could agree on in terms of consensus. So I took this paper to say this is the minimal, the minimal type of re-flex testing that needs to occur with the CBC, and each laboratory should feel free to add more which we have done.

And I'm sorry, I did have another comment. That related to Dr. Snyder from Worcester. It seems to me, you know, you're hearing a lot about we have grave concerns about generating quality CBC results, and if you work in a system where you have a distributed clinic site and access is an issue, because you're hearing the testing has major quality issues, should we not instead direct our effort at improving access instead through better courier service, better transportation, to get it to a laboratory that can generate good results instead of trying to send what we consider a problem prone method and distribute it out to locations where we're not comfortable people can do the tests correctly.

DR. ADCOCK: Dr. Gutman, it seems that for the waived testing, we cannot make a stipulation about training.

DR. GUTMAN: That's correct.

DR. ADCOCK: Do you feel that based on the summary that we've provided to you that this is

adequate information for you?

DR. GUTMAN: Yes, it's very helpful.

DR. ADCOCK: Shall we move onto question number 2 please.

MS. BAUTISTA: Question 2, Analytical. In performing CBC/Diff testing, laboratory professionals traditionally control for a variety of biological factors that produce analytical variation. These include cold agglutinins, rouleaux, osmotic matrix effects, platelet agglutination, giant platelets, unlysed erythrocytes, nucleated erythrocytes, megakaryocytes, red cell inclusions, cryoproteins, circulating mucin, leukocytosis, in vitro hemolysis, extreme microcytosis, bilirubinemia, lipemia, etc.

Please explain what data/information a waiver submission should include to address these or other analytical issues; or if these issues cannot be adequately addressed and a submission for waiver categorization, please explain why.

DR. ADCOCK: Would any of the Panelists like to begin the discussion?

MS. RICE: I'll say something.

DR. ADCOCK: Ms. Rice.

MS. RICE: I don't think you can. I think that all of these variables will come up as flagged

results. If you are going to a health fair, if you are going to a pharmacy to have your CBC done because you don't feel good, you're going to have a printout given to you of a flagged result. You're going to see a number there, but it will be flagged, and you're going to go do a Google search and see what this means, and you come up with 100 things. There's nowhere that says you need to go to a physician because this result is flagged. Nothing is going to make sure that you go a physician to have it followed up. There are too many variables there that a patient is met with when you're outside the clinical testing which waived testing is.

DR. SANDHAUS: I'd like to respond to that.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: Thank you. As we've heard, the state of the art automated hematology analyzers that are currently in use in laboratories generate many, many flags, and these flags do not specifically identify interferences. They merely suggest what interferences might be present, and then laboratories have procedures of what steps must be followed up on to assess the significance of that flag. And since that can't be done in a waived setting, there won't be follow-up at that site on that test result, my

recommendation would be that what would be a flagged result in a laboratory setting should be a suppressed result in a waived setting. A number should not be produced with a flag in a waived setting where that result cannot be followed up on appropriately.

DR. ADCOCK: Dr. Wang.

DR. WANG: I concur with that.

DR. ADCOCK: Dr. Kost.

DR. KOST: I agree but don't exactly agree because some of the flags are for very serious conditions. So perhaps rather than suppressing a result, it should say see your doctor immediately or something but there could be another level of esoterica involved if the software were good enough, i.e., appropriate direction of the patient.

DR. ADCOCK: Other comments? Dr. Bull.

DR. BULL: I think we're getting into a realm that is different in many respects from other waived tests in a qualitative sense, and that is a physician typically conducts a physical examination of a patient and based on that physical exam determines what tests to order. So the hematologist, it has been fairly traditional to use the full blown CBC as the equivalent of the physical exam. If you ask a hematologist what would they prefer, would they

prefer to be able to do a physical exam on the patient or just see the CBC, the answer I think most of them would give is I'd much rather see the CBC because it's my equivalent of a physical exam.

Now, what we're doing in this situation is we're taking what the equivalent of a physical exam is, and we're putting it in a waived setting where it's not going to be what a physician now uses to make diagnoses in the field of hematology. I don't have a problem with hemoglobins and hematocrits as waived tests. I think that they're very useful because they diagnose the presence of anemia or the absence of anemia.

CBC is, in my opinion, quite different, and I think the similarity to a physical exam for a general practitioner is probably apt, and under those circumstances, we're asking a machine here to do what a healthcare professional will normally do based on this data. And that is, I think, why we're having so much trouble determining what we do next under these circumstances in a waived setting.

DR. ADCOCK: Mr. Bracco.

MR. BRACCO: I guess this question is for Dr. Gutman and Dr. Becker. Are you looking for specific types of tests that should be run? We

already know that we need flex studies and we already know that we need the clinical accuracy studies. So from a general standpoint, I think we're all clear what's needed. Is this particular question asking what type of data should be included?

DR. GUTMAN: Well, yeah. This question, for example, would be helpful, you know, I think that there are slightly different variations in terms of feedback. So we're trying to get no leading feedback, but in this case it seems, you know, at least one suggestion on the table is what should be flagged. I'm making the assumption that everyone here thinks that everything here should be flagged. But I'm also hearing the fact that maybe even the flagging isn't sufficient. So when you summarize it, you'll tell me whether -- there are two emerging voices here. One is suggesting that there's a possibility of addressing these by making sure they all flag them, and the flags should probably say see your doctor, not suppress the result, but there's also a suggestion here that the flagging isn't really quite enough because the CBC has an unusual distinction in terms of its scope. It's a test that becomes a configuration that belies the ability to be waived. Am I hearing what you're hearing?

DR. ADCOCK: Yes, I do have another point for discussion. What would the Panel think about an abnormal result? I mean normally in a hematology laboratory, if the platelet count is low, that would initiate a review of the smear to ensure obviously no artifact. So what would we do in a waived setting then? Would any abnormal result be a flag and no result would go out and all this instrument would do would be provide a completely normal result if it is completely normal?

DR. NG: That would be my recommendation, and even with that recommendation, I would be worried about the false negatives that are showing up as normals. So I'm just not comfortable. And, you know, I can't tell you how many times a year somebody thinks -- I mean a patient is thought to have a normal platelet count, and you look at the smear under the scope, and there are no platelets and it's all histocytes, you know, it's DIC City and, you know, nobody's tumbled to it except for the hematology lab. You send out a false normal platelet count, somebody in a rip roaring TTP out there in the community, you know. You know, you've got a bad situation on your hands.

DR. ADCOCK: Dr. Kulesza.

DR. KULESZA: Right. Again, I think that my feeling would be that there are technological solutions through, you know, free hemoglobin that can potentially detect this, and I don't think that the cost issue that was brought up is something that I feel is our obligation to consider. It's up to the manufacturer to develop whatever it cost machinery and how cheap or expensive the technology might be. I think that I would want to see a more complete and exhaustive version of the potential pre-analytical as well as analytical variables that the machine would have to take under consideration.

And I would support -- completely I agree with Dr. Kost that there has to be a separation between a result that's say erroneous for the minor proportion of nucleated RBC. That could not be resulted, and a printout would say see your doctor. That would be very different from a real and tested result of say platelets of 7,000 because that is an emergency that I think action would require an immediate visit to a physician and immediate cause for medical attention. I don't know how one would handle that. I mean, I don't know how a critical result is handled in a waived setting. That is something that I don't think is possible to resolve.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: I think one of the problems is it's hard to know if it really is a critical result or if it's an erroneous result, and in a waived setting, I don't think you can answer that question. In the laboratory settings that I work in, I think that one of the most clinically important errors that we see in our hematology lab is a falsely low platelet count, and we haven't figured out how to solve that problem in the laboratory yet. So how are we going to solve it in a waived setting, and to have the result come out with see your doctor, when you're in your doctor's office, doesn't really make sense to me.

DR. ADCOCK: Dr. Wang.

DR. WANG: Again, this is a very comment test, I'm sure you all agree, and I really doubt that every single test is scrutinized by a medical technologist or a physician. Most of these tests are already automated, the results are released. Only those that are flagged and, according to my understanding, the machine comes with certain criteria of flagging the results. Then the lab director also builds in additional criteria to flag the results.

For example, since I'm not familiar with this, so I just vaguely remember if two values contradict each other, so there's something wrong, and that's also flagged. So there are a large number, I think in the hematology lab at our hospital, they build in 13 more criteria to flag the results. So when I say the results should be suppressed instead of released, that means that's an indication the patient should see a doctor sooner rather than later, and instead of trying to interpret this as erroneous result or abnormal result. So basically I'm trying to say is a lot of -- this test is done like 88 million last year or something like that. I'm sure most of them are not scrutinized, were not scrutinized by a technologist or a pathologist. Most went through the machine and the results were released. So it's -- my concern is those that were flagged, how do we deal with this. So if we can say the results are suppressed, so instead of giving a false result, it would say you need to take the next step and your specimen is abnormal and you should see a doctor. By abnormal, I don't mean that it has an elevated WBC or abnormal granulocyte count. By abnormal, I mean it refused the criteria flagged by the machine or by some other

additional criteria we designed.

DR. NG: But then, you know, thinking about the safeguards I put in place in my lab and auto verification is this close that I want to implement, but what I have in place are, before I release the result, California requires until I get out auto verification, CLS has to look at every value, number one, number two, the QC has to be in, number three, the delta check must be acceptable. That's the historical trend. Number four, my peer comparison on that lot of reagent with that instrument to my peers across the world must be within an acceptable range, and finally, I got to make sure my PT is acceptable. All that comes into play in my quality system before a result goes out. I don't see how a waived device would hold that type of information on an individual sample to know that's a quality result.

DR. KOST: A vexing problem for which probably there's going to be no certain solution at the end of the day, but ultimately, if you consider the historical trend of point-of-care testing, and I'll also make just a quite note on the fact that NIH now has funded four centers for point-of-care technologies of which we are one, and the primary push is to get these technologies up and going and

out into the primary care setting where the doctor take appropriate action.

So as the gavel falls today, I guess we have to remember that to assess ultimately whether a point-of-care device would do more good than harm, we would have to go to outcome studies, and this is a difficult issue when we try to bridge a moderately complex and fairly difficult and challenging thing, such as the automated CBC, et cetera, three part, five part diff.

But ultimately in various primary care settings, this is what would be needed, and I would recommend that the FDA consider implementing and asking for outcome studies in some of these more challenging cases of point-of-care technology.

DR. ADCOCK: Any further discussion?

DR. NORBACK: I didn't weigh in yet.

DR. ADCOCK: Certainly, Dr. Norback.

DR. NORBACK: As in the previous consideration, if the instrument can recognize every situation and then not give erroneous results that would be acceptable, we wouldn't want to lose what we have now where the professional recognizes these particular problems and then helps in the diagnosis and care of the patient, but I'm anticipating that if

we had an instrument that could recognize these, and then suppress the results, not give erroneous results, and then the next step would be to have another blood sample that would be looked at by a pathologist.

I have one more thing to add. These are relatively rare, and I imagine the emphasis of the instrument in the waived setting would be to do the majority of tests that didn't have such complex results. So problems like this, it's very important that the instrument recognizes that the problem is there and incorrect results cannot be given, and I've already given the example, blas cannot be lymphocytes, but if the instrument could do this and then just state that this instrument cannot offer any information on this sample, perhaps it is still doing a good thing.

DR. ADCOCK: And let me ask you, Dr. Norback, what would you do with a very elevated white count? Would you have the instrument report a result?

DR. NORBACK: Well, with an elevated white cell count, I think we do have to look at the cells that are present, too. So that will get into the discussion when we talk about its accuracy for the

different components of the differential, but let's -- I think the simple answer would be that if the instrument could reliably give a high white cell count, it should be allowed to report that, and then further information would follow from another analysis.

DR. ADCOCK: How about a low platelet count?

DR. NORBACK: I've suggested that that would be part of the challenge of the instrument. It would have to be accurate enough to give an accurate low platelet count. So a platelet count of 10,000 could not be reported as 30,000. But if an instrument can accurately give a platelet count of 10,000, and I'll also repeat that these hypothetical capabilities of the machine, you know, that it would be quite a challenge I think to identify every problem that we would put on a list that had to be identified.

DR. ADCOCK: And I'm not trying to put you on the spot, but perhaps another question is could that 30,000, if it were an accurate platelet count be reported without a -- verification that it's not erroneous?

DR. NORBACK: All of these need careful

consideration. I don't want to compromise the care that is now given to the patient based on the robust analysis of the professionals in the laboratory. So somehow I would want to keep that component also and perhaps with a high or low platelet count would require review before being reported. It's a good question. I think these are things that I would want to think through all the clinical situations that need to be addressed.

DR. ADCOCK: Dr. Kost.

DR. KOST: I may be out of order, but I'd like to read into the record another paper please, and I'm the first author. This was published in Clinica Chimica Acta, this year, 2008, Volume 389, pages 31 to 39. It's not right on the subject today. It is called "Evaluation of Point-of-Care Glucose Testing Accuracy Using Locally-Smoothed Median Absolute Difference Curves." There's a second paper in press for diabetes therapeutic and technology using the same, we call it LSMAD curve technique, and what we've found in rather large data sets is that the existing technologies that are already out there are not that accurate at the low and high ends, and this comment by Dr. Norback specifically and the questions address the low and high ends. I don't

personally see how the model which has been presented of testing 360 samples will do it, how that one will have sampling error, and it won't pick up all these things even if all the circumstances would lend themselves toward it.

And the LSMAD curve technique, I think while it hasn't been, could be applied to this. I would recommend that the FDA consider the math behind this. It's actually quite simple, but very, very visual and highly clinically relevant in discerning problems at low and high ends, specifically clinically relevant ranges. Thank you.

DR. ADCOCK: If I can try to summarize at this point. I think the Panel generally believes that there are many issues that would face an instrument pertinent to its proper analysis of a CBC sample, and that an instrument would have to have very secure fail-safe mechanisms in order to account for these. There is a significant issue as to what the instrument would do to identify these in a way that the report would reflect the issue properly. So the FDA would have to be very certain that they put enough fail-safes and identified enough of these analytical issues such that the testing would account for them. And there's some serious question as to

how many samples would have to be evaluated, and there's concern that 360 would not be adequate to exemplify these potential analytical interferences.

The Panel also has some question as to what results would be reported and what comment would go on the report when they're either abnormal results or when there is a potential interference.

DR. ADCOCK: Other questions?

(No response.)

DR. ADCOCK: Dr. Gutman, do you think that's satisfactory?

DR. GUTMAN: It's very rich discussion. Thank you.

DR. ADCOCK: Question Number 3.

MS. BAUTISTA: Question 3, Post-analytical. Depending on the particular test system involved, CBC/Diff testing can report results for a wide range of hematologic analytes and in a wide variety of use settings. Operators in moderate or high complexity labs are trained to control potential post-analytical sources of error using a variety of techniques, including evaluation of microscopic slides.

Question 3. In order to ensure that there is no unreasonable risk to the patient from incorrect test results, are there particular CBC/Diff analytes

or combinations of analytes that are more appropriate than others for use in a waived test setting?

DR. ADCOCK: Would any of the panelists like to open discussion on this question? Dr. Bull.

DR. BULL: It seems to me that one of the most useful would be just simply a total white count if that could be enumerated accurately reproducibly. I think the chances of that leading people astray are perhaps less than with platelet counts and with three part and five part diffs. But to reiterate once more, question 5, how should the lack of trained operators in identifying post-analytical anomalous or incorrect results be addressed, I would strongly recommend that the FDA push or the manufacturers or both to getting some sort of oversight and some sort of minimal training because I don't think it's going to be physically possible to generate a machine for these sorts of settings, most of which are fairly low volume and the machines are going to have to be fairly low cost or they're not going to penetrate the market, if you have to rely on the machine entirely for everything.

DR. ADCOCK: And I'm not certain that's an option.

DR. BULL: Well, it isn't an option now.

I'm just simply saying that until it becomes an option, I don't think it's going to be possible to release more than a very, very simple white cell differential, and I think we should limit it to maybe just a total white cell count until something like this can be addressed.

I think the waived test setting, originally we thought it was only going to be hemoglobins, hematocrits, pregnancy tests and urinalysis dipsticks. We're now told today that we have over 60 -- 100. We now have 100 waived tests. That's a completely different question than the one that was faced originally when this was set up, and it was decided that no training was going to be needed or at least no training. We were going to work with the situation in which the operator had no responsibility and the machine had everything.

We're now getting into an arena where that's probably not going to be operationally or physically feasible because to generate a machine that is fail-safe with somebody who has no training is a lot more expensive than generating a machine with somebody who has had a minimum amount of training. And I think that if the Panel can be of help to the FDA in this regard, one of the things it

could underscore is that we're coming to the point where at least minimum training and oversight, proficiency testing and quality control, are going to have to be instituted in waived tests or we just simply can't proceed with anything that's more complex that the ones that we've got right now.

Now, I may be wrong. It's possible that coming downstream, we're going to have machines that can do all of this, you know, maybe they're going to have artificial intelligence of a sort that will make operator intellect completely disposable. But I think that's going to be fairly expensive and I don't see in the large laboratories now. Typically it takes another 8 to 10 years for the machines to move from large laboratories to small ones. So, in our lifetime at least, I don't think it's going to be possible to do this unless we can get some minimal amount of training on the people who are going to run them.

DR. ADCOCK: May I ask for other Panelists to weigh in question number 3?

DR. KOST: A question for Dr. Gutman. Is the thrust of this question what is clinically useful, what combination or looking at the technical side of it?

DR. GUTMAN: No, no. I actually think that Dr. Bull's answer, we were trying to understand the spectrum, you know, a total white cell count, white cell count and platelets, white cell count and differential, three part, what combinations might seem more comfortable to the Panel. So now you're allowed other choices besides Dr. Bull's, but he gave an answer to the question that was intended.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: I'd like to offer another answer to the question. I actually had to read that question many times at different times, different days, to try and figure out what you were getting at with that question. It is confusing.

I think that, you know, if we're going to call it a waived CBC, to be called a CBC, it needs to provide information about the hemoglobin, hematocrit, which I really consider the same thing, the white count and the platelets. I mean, I think those three components need to be there, and I think with the white blood cell count, I think you would really need to have an absolute neutrophil count as well. I'm just anticipating the types of settings that this would be used in, and if it's going to be used in an outpatient oncology setting and, of course, once it's

waived, we don't have control over what settings it's used in, it might be used in a variety of settings, but certainly in that setting, it would be imperative to have an absolute neutrophil count.

DR. NG: Just a comment on Dr. Sandhaus' comment. It's exactly in that setting, the neutropenic patient going in for chemotherapy, that this device has the greatest risk for patient harm if it gives the inaccurate result. So that's why I still remain uncomfortable. I think I'm willing to go with a total white count. I think I'm willing to buy into that but --

DR. ADCOCK: So with hemoglobin perhaps.

DR. NG: We already have a hemoglobin. So I don't pay attention to that anymore. So the new thing would be the total white count.

DR. SANDHAUS: I agree with you.

DR. KULESZA: I agree completely, and I think that the corollary of this approach would be that if one limits the number of analytes, one simplifies the task and lowers the perspective cost for the manufacturer and limits the number of instances where if I have to distinguish between neutrophils, high, low, versus lymphocytes, then the number of constraints that are analytical as well as

pre-analytical goes down. So the simpler the better.

DR. ADCOCK: Dr. Kost.

DR. KOST: The commentary flows into the next question, which is about critical values, and having done several surveys, national surveys in this area and seen some of the more recent contestable results, I'd like to make a comment on neutrophil counts and such like, especially in the low range.

Earlier one Panel member suggested that maybe plus or minus 200 is an absolute error band for this would be acceptable but, in fact, for absolute neutrophils, sometimes 100 or even lower error band is necessary due to the fact that you'll be on one side or the other of a hospital or an institution, such as a primary care networks critical value alert list, and therefore the technology that we're talking about today would have to exclude reporting results that are low but then possibly result in harm not getting the number out, but the number per se could be very, very excruciatingly important and litigated within the system if it didn't accurately report 400, 500, 600 or whatever.

So I didn't find any of the error tolerance concepts, the models that the FDA has presented so far to be particularly satisfying.

DR. GUTMAN: Could we wrap up 3 and make -- but I appreciate, I appreciate the overlap between the questions but we are sort of by Robert's rules bound to a protocol. So perhaps we could wrap up 3 and go to 4.

DR. ADCOCK: Dr. Aziz.

DR. AZIZ: Actually I have a question. Maybe Ms. Yost can answer it. What is included in the CBC? For that CBC code, what is included?

MS. YOST: Again, I'm not a Medicare expert, but I think there are several iterations of CBC codes depending on what the parameters are for CBC codes.

DR. GUTMAN: For the purposes of this discussion, we wouldn't hold you to a rigid definition. The whole purpose of this discussion is, as I suggested before, is to understand if there might be some -- is to ask you to define what part of the CBC you're more comfortable with.

DR. AZIZ: The reason for my question is like if we're only going to have like an analyzer can only run a WBC, RBC and platelets, you know, is that acceptable when it comes to -- is that a CBC?

DR. GUTMAN: Well, I would not call that a CBC, but it's, you know, the question is, is that a

waivable combination of devices. So it's irrelevant whether it's a CBC or not, and the reimbursement issue is completely different whether you pay less or more.

DR. AZIZ: I'm not asking about, you know, financially how much are you going to make out of this, but like, for example, we just added some parameters to the CBC. Like the RBW, I mean that is a relatively new one. So what is considered a CBC? Like, you know, when you say complete, you know, can you have a basic blood count, a BBC. I mean is that --

DR. GUTMAN: Well, I would argue that that's not a CBC, but I guess it's less important to me to understand what you're calling a CBC. It's more important for us to understand which parts of the CBC are waivable. So I wouldn't focus on the semantics. The purpose of this question was to understand the analytical mix of interests, not the nicety of the exact definition. I agree with you. I think it becomes awkward because the expectation for a CBC right now is probably a little bit more like a Cadillac and less like an Accord.

DR. ADCOCK: Thank you, Dr. Gutman. Dr. Ng.

DR. NG: I thought I'd go out on a limb and tell you what I would potentially consider waivable would be a total white count and probably a percent neutrophils.

DR. ADCOCK: Mr. Bracco.

MR. BRACCO: I'm just curious from a practicality standpoint how this would play out in the real world. It sounds like a partial waiver that you're now talking about. So what happens in the real world? A sample comes in, a professional has to walk over and run that one. Another sample comes in, and a non-professional could run that one. How many of these, I don't know if you know the answer to this, but what percentage of these CLIA-waived devices have a scenario like this where they're partially waived?

DR. GUTMAN: Yeah, the reason we have a Panel is that this is a unique, actually sort of first of the kind for us. So I'm not sure we have any precedent where you have such an interesting mix of, of analytes that seem to play against each other. So I'm not sure I have much history to draw on.

MR. BRACCO: It sounds like a logistical nightmare to me in a laboratory to have a partially waived device.

DR. ADCOCK: Dr. Bull.

DR. BULL: I think we've come back to my original point that the CBC for doctors that are interested in or specialized in or have a patient that's suffering from diseases of the blood is in some sense analogous to a physical examination. It's not a test as much as it is the way you start thinking about this patient with hematological problems.

DR. ADCOCK: Before we summarize for Dr. Gutman, I've not heard any consideration about platelet count. Would people like to take platelet count of the waived category?

DR. KOST: I specifically excluded it from mine because I have a long experience with platelet counts starting actually with the realization, with the very first platelet counter that we were running across patients who had a very low platelet count that appeared perfectly healthy. To give you an anecdote, the first person that this occurred on was at NIH, and it was Director of Nursing Services, and she was perfectly normal, but we were using the very earliest platelet counter and fed out a thrombocytopenic diagnosis on her, and boy, did we hear about that.

So EDTA antibodies that cause platelet agglutination and EDTA are a real problem and has stayed with us ever since. And so I don't know how you deal with that in a waived setting. I mean, you're going to turn out maybe two to three percent, maybe higher than that, of thrombocytopenic diagnoses if you let these machines loose in the way of setting without anyway of cross checking them, and those two to three percent of patients are going to be very nervous until some doctor checks them over and says, well, no, you're not dying of leukemia. You just happen to have an otherwise antibody that isn't going to cause you any other problems. So forget about it.

DR. ADCOCK: Very good. Dr. Sandhaus.

DR. SANDHAUS: Well, the question as you phrased it, should platelet count be excluded as a waived test, I think that's how you put it, I agree. I do not think the platelet count should be considered waivable. The remarks that I made earlier were simply to indicate that if you don't include a platelet count, you really can't call the test a CBC.

DR. ADCOCK: Very good. Dr. Ng.

DR. NG: What if I play devil's advocate? What if your platelet count was -- is it CD61? What if it was a CD61 based method? I mean, assuming you

can deal with all of those pre-analytical issues.

DR. ADCOCK: Would anybody --

DR. SANDHAUS: Yeah, actually I can address that because we did a study using the reference method for platelet count you're referring to, which is a flow cytometry method that uses two monoclonal antibodies to identify platelets. You know, even with the reference method, you don't obviate or circumvent the problems with pseudo thrombocytopenia. You still have the same error can occur.

DR. ADCOCK: Dr. Wang.

DR. WANG: What if we include it but set a relatively high threshold to suppress the results? If it's below a certain threshold, then the results are suppressed.

DR. BULL: Well, I think you're going to run into the same kind of problem with the patient. You're going to tell the patient that we don't know exactly what's wrong with you, but there is something wrong with your blood, and the first thing that a patient thinks of is leukemia, and until they get a blood count that puts their mind at rest, you give them some period of time, it could be a few hours, it could be two or three days, they know that there's something wrong and they don't know what it is. I

think the Panel is sort of obligated to consider patient's nervous status between the time the machine refuses to give them a result and the time they discover that this is perfectly all right. Right now, of course, it usually is taken care of before they even get the results. So -- but we're in a waived setting, and we're not going to be able to do that.

DR. SANDHAUS: You know, I think we're really getting to the meat of the matter now as to which components are waivable and which are not, and we're deconstructing what we know as the CBC, and one of the things that I've become exposed to through my involvement at point of care is the assumptions that non-laboratory personnel make about laboratory testing, and it's been a real eye opening experience to me. And what I have a lot of concern about is if certain results are not reported, they're suppressed for example, because the result is questionable, I wonder what assumptions the caregivers might make about those results that are not reported.

Now, just to give an example of this to an unrelated area of point-of-care testing, which is cardiac enzymes, we were just involved recently in implementing point-of-care troponin testing in our

emergency department, and during the two years during which we discussed implementing point-of-care troponin in the ED, no other cardiac enzyme was ever mentioned in that discussion, yet nevertheless when we brought up the test in the emergency department, the director of the emergency department was totally surprised that that did not include other cardiac enzymes. That's just an example of the assumptions that get made that aren't communicated.

And a particular concern that I would have with CBCs is that if a white count and hemoglobin hematocrit were produced but no platelet count appeared, and the other results were normal, I would expect based on my experience that there would be assumptions made that the platelet count is probably normal, too, and 99 times out of 100, that would be correct.

DR. ADCOCK: That's an excellent point, Dr. Sandhaus. That by omission, we may be giving a false impression.

DR. SANDHAUS: Correct.

DR. ADCOCK: Other comments?

(No response.)

DR. ADCOCK: To summarize, the Committee generally believes that the combination of perhaps

hemoglobin with total white cell count might be the most appropriate for a waived submission, possibly to include a percent neutrophil count, but wants to make note that omission of other results may be problematic because of the assumption that those results that are not reported may be normal.

Is that an adequate summary, Dr. Gutman?

DR. GUTMAN: Yes. Thank you.

DR. ADCOCK: Shall we move on and take one more question before the break perhaps.

MS. BAUTISTA: Question 4. Should there be specific provisions for follow-up of some results, i.e. critical/panic values, or other post-analytical measures that should be considered for waived CBC/Diff testing? Please explain.

DR. ADCOCK: Dr. Ng.

DR. NG: Can I just ask a favor of Dr. Kost, because you have the Barnes paper with you, of that 12,786 CBCs, could you tell us what number and percent were flagged, and then upon review what percent were true positives? That would give us a sense of the post-analytical stuff faced by professionals today, which I would think would be the minimum that would be seen with a waived test.

DR. KOST: Okay. Total samples, you want

numbers or percent?

DR. NG: Both.

DR. KOST: Both. Okay. Total samples 13,298. This is in Table 2 on page 85. True positives, 1,483, 11.20 percent. False positives, 2,476, percent 18.60. True negatives, 8,953, percent 67.30. False negatives, 386, percent 2.90. I didn't check to see whether these figures added up to the total sample or percent. We'll give them that.

DR. NG: So as I hear those numbers of all of the ones that are flagged, and I'm just going to call those generic positives, roughly 40 percent of those are true positives and 60 percent would be false positives, and that constituted a total of 38,000, about 25 percent of the total sample volume. And then all the negatives, 3 percent of those would have been false negatives. So that would be in a best-case scenario.

So what I would expect for a waived device, maybe I'm wrong, but that it would mimic what we're seeing in the laboratory or be worse, and what we're seeing in the laboratory is that about 25 percent opted out because of a flag, and of those that are flagged, about 40 percent of those are true positives, 60 percent are false positives. Of those

that do not get a flag, there would be 3 percent at a minimum false negatives.

DR. ADCOCK: Is that too much now?

DR. NG: So what's the follow-up? Like what's the follow-up. You have a flag, and you know 40 percent of those are going to be true positives, but 60 percent are not, 60 percent are errors. What should the follow-up be? And then with the negatives, how are you going to find that 3 percent needle in a haystack, that report is a normal value but, in fact, they're incorrect?

DR. BULL: I assume that because these tests are being done for patient care, that we're going to follow up on all of the positives, whether false or true. Why else are we doing the test?

DR. ADCOCK: So would there be a recommendation then that it be followed up with a more conventional CBC? And if so, in what timeframe?

DR. NG: So you can capture the positives. How do you capture the negatives, the false negatives?

DR. BULL: I don't think you can capture the false negatives. I think you just have to live with the fact. I'm sure there'll be even more in a waived setting, but since we're not capturing them

now, I don't see how we can impose tighter standards on waived settings than we are imposing on professionally run laboratories, but this does mean that a lot of those samples, I guess, something like 25 percent of them, are going to require follow-up, and many of those in view of our previous discussions are going to be locked out. So it depends on why they were positive and how positive they were. That means that about one out of every three or four specimens is going to have to be redone by somebody else. Is this really going to benefit patient care?

DR. ADCOCK: Dr. Kost.

DR. KOST: A comment. It seems to me in the waived setting it would be a miracle to get only 2.90 percent false negative, but on the other hand, to avoid the doom and gloom setting that we might find ourselves in, it would be some photonics and other technologies coming. I don't know how clever industry will be on this one, that have laser tweezers and separate cells directly, and a lot of what we've been talking about such as interference become moot and so on and so forth. So over to you for a summary.

DR. ADCOCK: Are we ready?

DR. SANDHAUS: In a waived setting, I don't

know how we can enforce follow-up. You can't enforce compliance with a request or recommendation for follow-up.

DR. ADCOCK: Yet the testing might identify a critical result.

DR. SANDHAUS: Well, if you're doing it in a waived setting as a point-of-care test and you get a critical result, then that's a final result. A point-of-care result is by definition, it's auto verified. It's out there. So if you're not going to act on it, then why do it.

DR. ADCOCK: So what if this waived instrument identified a critical result, yet it didn't report -- it suppressed the result. Then there's really no way for the user to know that it's truly a critical result versus an erroneous result.

DR. KULESZA: We would have to prevent it as the evaluation proceeds and the FDA looks at this, there would have to be a distinction made, that there are critical results that are not error, and those are reported as panic values. And then there are results that perhaps might be error, or we see something that is not life threatening based on our best assumptions, that could be reported perhaps as at least follow-up later or with whatever caveat

there is.

I am a little bit also concerned about the negative, and the way we are approaching the false negatives. Why not insist on a higher stringency technologically for that instrument? We know that it's going into a waived setting. What stops us from saying to the industry, please develop better means such that the false negative issue is not as important because we're putting it somewhat into the screening realm as opposed to a diagnostics realm by letting it be waivable, I understand.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: Well, I've been asking industry to solve those problems as well so that they can put those instruments in our laboratory.

DR. ADCOCK: Dr. Wang.

DR. WANG: Since I deal with cervical cancer screening every day, I have to say false negative results are inevitable. It's just how much we can tolerate it. I'm not aware of any medical test that has a 100 percent sensitivity.

DR. ADCOCK: Any additional comments from the Panel?

(No response.)

DR. ADCOCK: If I can try to summarize

then, and I hope I've captured everybody's thoughts correctly, there would have to be specific provisions for some result because the instrument can generate critical or panic results. In addition to that, there would also be the potential for erroneous results, and these would require follow-up.

All right. I think at this point --

DR. KOST: Which question have we answered by the way referring back to Robert's rules.

DR. ADCOCK: Question Number 4.

DR. KOST: 3 and 4.

DR. ADCOCK: Yes, and we'll come back to question number 5.

So I believe at this point it's 3:00. I'd like to propose a 15-minute break and invite everyone to please return by 3:15 so we can begin again.

(Off the record at 3:00 p.m.)

(On the record at 3:15 p.m.)

DR. ADCOCK: I'd like to reconvene the meeting please at this time.

I believe at this time we're now on question number 5, and I would like to ask Ms. Bautista to read the question for us please.

MS. BAUTISTA: Question 5. How should the lack of trained operators in identifying post-

analytical anomalous or incorrect result be addressed?

DR. ADCOCK: Would anyone on the Panel care to -- Ms. Rice.

MS. RICE: If they aren't trying, they probably aren't going to recognize that there are incorrect results and to me training is the only way to handle this.

DR. ADCOCK: Dr. Bull.

DR. BULL: And I would answer this question the way I've answered this question a couple of times previously, and that is I think that the FDA and the lobbyists for the manufacturers should get together and see to it that there is at least a minimum amount of training. I don't see inherently any reason why a person performing a waived laboratory test shouldn't be required to have a few weeks of training so they recognize the very obvious things about blood. My concern is that if you can pull in a bookkeeper or a receptionist with no knowledge whatever and set them in front of a waived test device, then it's our responsibility to make sure that we have a technological fix for all possible occurrences that might eventuate because this person doesn't even have the minimum knowledge of how to handle blood and

blood specimens.

In California, we're required to train our phlebotomists, and we can explain to them what blood is and how it sediments and why you don't squeeze a fingerstick or heelstick vigorously, and if that can be done, it seems to me that sooner or later if this waived testing is going to increase, which obviously it is, and get bigger and bigger and bigger, that there should be a minimum amount of training required of the operators, and I know that that isn't part of our purview today, but like Ms. Rice, I would say that we should address the lack of untrained operators by training them.

DR. ADCOCK: Dr. Bull, if I may ask some clarification. If the testing that moves forward is white blood cell count only, do you still feel that training is needed?

DR. BULL: Yes. I still feel that a person who is going to manipulate blood needs to have at least the knowledge of the phlebotomist, and that would require that they understand that blood sediments, it needs to be mixed, before you present it to the machine. And it needs to be mixed more than once, and we actually did a paper some years ago on how many times you have to invert a test tube

that's been fully sedimented to get the red cells, the white cells, and the platelets evenly distributed and published the results. It turns out about four complete inversions are required with a fairly large air bubble until you've got the specimen mixed.

Now, if you're going to allow a person who doesn't even know that, to present blood to this machine, then you've got serious problems that we don't really need to deal with. If we could get Congress, and that's why we have lobbyists, and if the lobbyists and the FDA got together, I think they could do something about it.

DR. ADCOCK: Other comments before we summarize? Dr. Kost.

DR. KOST: Could I ask Dr. Gutman what his opinion is on that? Can we change waived or can't we? Is there a --

DR. GUTMAN: Well, we certainly can't. Congress could. It probably wouldn't be a good idea for us to get together with the lobbyists actually, but the recognition is one that's interesting and certainly is appropriate for discussion. Again, I don't actually personally deal with Congress very often and try and make it, in fact, as infrequent as possible. But I understand the point being made.

DR. ADCOCK: Dr. Norback.

DR. NORBACK: One of my points previously was that if we talk about using analyzers in a waived setting, we can't be talking about the current instrumentation because the instrumentation and the testing is not simple, and it is prone to producing results.

So my hypothetical situation was that if the manufacturers can identify and produce instruments that will recognize all of the mistakes so that we do not have falsely low platelets and we do not have falsely normal platelets, then we're not dealing with erroneous results, and my suggestion was that the instrument had to be challenged, and it would be very difficult but probably not conceptually impossible for enough different approaches to analyzing cells could come up with an instrument that was really very, very capable at preventing erroneous results.

So my hypothetical situation was is that the instrument would not be marketed. It would not be used in a waived setting until it had been clearly demonstrated that the instrument would not produce erroneous results.

And then I'll extend that a bit and apply

it for when we get to another question of what should be the level of allowable error be. You know, I think the error should be very stringent in a waived setting when professionals are not reviewing the result, but we're not talking about instruments that we have now. We would be talking about instruments that could have a very, very low tolerable error, and then we would be answering the questions differently. You know, if we had instruments that did not produce errors, then we would be reporting results out with a great deal of confidence.

DR. ADCOCK: Yes.

DR. KULESZA: I agree completely with what was said here, but let me just emphasize that looking at the prior questions and looking at what FDA had presented as the necessary clinical testing of the devices that would qualify for it, currently understood the waived category, the testing would have to be much more stringent than I think was presented here in the sense of challenging the instrument and analyzing its performance.

DR. NORBACK: I don't think we really established the criteria for testing. We just said it had to be very, very stringent so that errors did not occur.

DR. ADCOCK: And do you think it's therefore given what you've proposed, if the instrumentation were that sophisticated, could it be operated by non-trained personnel?

DR. NORBACK: Well, that's the hypothetical situation, that the instrument could be developed, very, very hypothetical, that would meet all of the criteria that we look for in a professional setting, and I'm not saying that it can be, but clearly if an instrument can give us two values, they should be reportable.

DR. ADCOCK: Other --

MR. BRACCO: I'd also like to just comment once again that we need to be careful with this training piece. It really doesn't say in the guidance that individuals don't need to be trained. It just talks about technical and specialized training, and it really talks in regards to troubleshooting. So the fact that someone needs to be trained doesn't necessarily mean that the device can't be waived. I just think we all should make sure we understand that.

DR. ADCOCK: I do think the point has been made, however, that the turnover of personnel that might be operating the instrument is great and that

if the instrument does come with some manufacturer's instructions, that they may not be available to the individual running the instrument, and I think those are very pertinent points.

So to summarize, if I may, given the current instrumentation as we know it, we don't feel it would be possible to have untrained personnel that could identify the post-analytical problems or that could identify the problems, but if the instrumentation were to be advanced such that there would be fewer inherent errors, then it would be potentially possible to have untrained personnel or not formally trained personnel. Perhaps I'm using incorrect terminology.

Is that summary sufficient?

DR. GUTMAN: Yes. Thank you.

DR. ADCOCK: Question Number 6 please.

MS. BAUTISTA: This is Question 6a, Performance. According to the 2008 FDA CLIA Waiver Guidance, for analytes that have existing performance limits for professional use, i.e., those listed in the CLIA 88 regulations, the published limits should be used to define boundaries of the allowable total error zones. These limits are express in CLIA 88 as criteria based on the fixed percentage difference

from the target value.

For the analytes listed in the table below, CLIA 88 Regulations provide the following limits for acceptable performance. And then there's the table.

Question 6a. Do these appear to be the correct ATE target values? Please discuss.

DR. ADCOCK: Would any of the Panel members like to -- Dr. Ng.

DR. NG: Well, I go back to the data from Plebani's article. In looking at the copy, there are 116 references that are summarized in there, which, you know, I'm naïve, but maybe at face value these are achievable ATE levels which seem to be much narrower than what are the CLIA acceptable limits. So I'll throw out an opening proposal that we should consider reducing the acceptable limits to somewhere near the upper limit of variability as identified by Plebani, and that is slide number 19 in Dr. Russek-Cohen's presentation.

So just to read that out, the white count I'll propose plus or minus 10 percent, the red count plus or minus 2.5 percent. I'm sorry. I'm adjusting. This is higher than what they reported. So I'm giving a margin of error. The hemoglobin should be plus or minus 2.5 grams per deciliter and

platelet count plus or minus 15 percent.

DR. ADCOCK: And, Dr. Ng, do you feel that these allowable error rates would be consistent across a reportable range?

DR. NG: No. I think it would be over, I don't know, the midpart of that linearity range but at the high end and the low end. The high end, a small percent is a large number. So you might want a smaller percent. I don't know. I'd go with the statisticians. I believe at the low end you definitely want to go with a constant number. I wouldn't choose that. I would let them choose it.

DR. ADCOCK: Dr. Norback.

DR. NORBACK: I also think that the allowable total error should be more stringent, and it's just I think meaningful to approach it, you know, analyte by analyte and then look at low levels, normal levels, and high levels, and for neutrophils, lymphocytes, and platelets, low levels are very important, and the total error has to be very small, and then for other analytes like -- well, platelets for example, we have to be able to discern clinically important levels at elevated platelet levels. So we just have to make sure that the total error is stringent enough so that one clinically important

value can be separated from another one. And it's easier, I think, for us as consultants to give them absolute values just based on our clinical experience as to what would be acceptable.

DR. KULESZA: Platelets would be particularly challenging not only at the higher ends because a lot of decisions whether or not to perform core biopsies or go with a finding of aspirations, transcutaneous or percutaneous, are based on the ranges between 50 to 100. Now, the guidelines not necessarily support that, but that is what is used clinically, and different physicians practice differently. A narrow rate of 25 percent in the range of 50 to 100 would be totally unacceptable because those would be decisions made on the spot, whether to go for a core or not, and the consequence could be devastating in terms of bleeding complications.

DR. ADCOCK: Additional comments?

(No response.)

DR. ADCOCK: So, Dr. Gutman, if I may ask, did you want us to try to develop these numbers for different ranges or give you a consensus opinion as to what is needed?

DR. GUTMAN: Yeah, I think a consensus

opinion would do. I'm not sure you need to go through -- that would be asking a lot to go through the three ranges. So some kind of general direction would do.

DR. NORBACK: I also want to add that whatever stringent allowable total error that we would set for each parameter, then the instrument should be challenged for that, too, and if the instrument cannot produce that, then it's not going to be on the market giving us incorrect results in a waived setting.

DR. ADCOCK: So if I can just reiterate what you said, the instrument would have to meet these error rates in order to be acceptable.

DR. NORBACK: Yes. It would be, you know, it would be one of the major deciding points as to whether development of the instrument could go forward. It would have to produce very stringent results, very accurate results with a very low total error. And it seems like the easiest way to test that would just be to challenge it with a number of clinical samples.

DR. ADCOCK: Dr. Ng.

DR. NG: You know, there was a thought, I'm probably dating myself here, that the percent

allowable error should be no more than 25 percent of the physiological variation. Is that still a valid concept, number one? And if it is, how do these ranges fit with what's known about physiologic variation in each of these parameters?

DR. BULL: There was considerable effort to take a look at it, because obviously if your physiologic error is very large and your analytical error is very small, the physiologic swamps it anyway, and for hemoglobin, for instance, the daily variation can, in normal individuals, it's typically somewhere between 5 and 7 percent, and in sick individuals, it can go as high as 15 to 20 percent. Well, if your daily physiologic variation is that large, you know, there's not much point in holding your hemoglobin to plus or minus 2 percent because it depends on what time of day you drew the sample. I don't know. I haven't followed the literature as to -- but that is a consideration that probably we should put on the table, suggest that in going forward, that we take a look at that because there's no point in holding manufacturers to an analytical variation that is some small fraction of the physiologic variation, and the figure of 25 percent was one that we came up with years ago, and I have no

reason to believe -- I think it's still valid.

DR. ADCOCK: Dr. Kost.

DR. KOST: Well, at the risk of self-annihilation, I'll suggest the straightforward things first and then just spend a moment on others.

I don't think that the CLIA concept, the proportional error per se, is really valid in this context. So that's something we need to get rid of, but that's already been addressed earlier. Also with evidence, we really don't have evidence based error tolerances per se that we can apply today, and I realize that in the document I was given, which is your release, January 30th, you do have the model that you've shown throughout the day that I would strongly recommend changing this format to a modified Bland Altman portrayal of same, which would be the difference on the Y axis between the point of care and the reference device and then the reference device only on the X axis to cover the entire clinical span.

In what you gave us as questions, now I'm going to be overruled for Robert's rules, but later you show and Dr. Gutman said we don't necessarily need to dissect the low, medium, high, et cetera, et cetera, but you've suggested that be done, and the

locally smoothed median absolute technique which we've invented for this takes a band and moves it through the entire range of the analyte, the entire clinically relevant range, and particularly nicely I think, and graphically highlights errors in the dangerous low and high zones. So I would recommend that you at least give it a try and see what you think of the theory and technique. Thank you.

DR. ADCOCK: Other comments from the Panel at this time?

(No response.)

DR. ADCOCK: All right. In summary then, the Panel generally feels that these allowable errors should be stringent and perhaps more stringent than CLIA 88 regulations, but there are some very important caveats to that, that the FDA consider the physiological variation and perhaps consider another method for evaluating the error, and it's been proposed that the locally smoothed median absolute difference curve analysis be considered.

DR. KOST: If I could make one comment. It's not something in lieu of what you've already suggested conceptually. In the paper, you'll see that we used for, and this is the glucose analogy, ISO15197, with the 20 percent error band above 75

milligrams per deciliter and 25 milligrams absolute below 75 milligrams per deciliter, and there are further definitions in the paper to identify discrepant values we call them, when you can flip flop back and forth, class 1, class 2 discrepant values which will critically affect decision-making, clinical decision-making. And then LSMAD curve analysis comes to play with that as a partner but not to replace above at all. So I'm not suggesting at all that this be replaced, just this be reformatted.

And the point of it all is that at least in the glucose area, not germane to today's discussion, the clinicians are saying we just don't like these error tolerances. They're too liberal. We want to tighten them up considerably. We just won't want devices anymore at the point of care that are possibly inaccurate and 20 percent, 10 percent is just way too liberal in terms of error tolerance. I've always said point-of-care testing is not an excuse for inaccuracy. Thank you.

DR. ADCOCK: Dr. Gutman, is that sufficient?

DR. GUTMAN: Yes.

DR. ADCOCK: Thank you. If we can move onto the next question.

MS. BAUTISTA: This is 6b, limits of erroneous results represent results for which the error is large enough to present harm to a patient. We have a table. Do you want me to read the table?

DR. ADCOCK: No.

DR. BAUTISTA: Okay. Question 6b. For each analyte, what is the maximum error that would not endanger a patient's health?

DR. ADCOCK: Would anyone like to initiate the discussion on this?

DR. NORBACK: Conceptually I think it has to be very close to the ATE or the allowable total error.

DR. ADCOCK: Other opinions?

DR. NG: I would look at this more as categorical limits instead of continuum. Maybe I'm looking at it wrong, but I would look at a hemoglobin, I don't know, if it's below 6 or greater than 16, you know, and a white count, ANC less than 500, absolute neutrophil count less than 500 or total white count greater than 40,000. I could go to 100,000. That's how I was looking at the LER.

DR. ADCOCK: Dr. Norback.

DR. NORBACK: Likewise, the allowable total error should also be different. It should not be

continuous, but it should be different for low levels, normal levels, and high levels for each analyte.

DR. ADCOCK: Dr. Kost.

DR. KOST: I'd just like to make a comment in regard to low, mid and high. These may not necessarily correspond to where clinicians do their decision making. So I think I would recommend that the FDA look at some of the decision levels per se and make sure that they don't have to peculiar idiosyncratic concepts that don't agree with decision levels. It doesn't make any point to have a break from a constant, fixed error bar to a proportional one right in the middle of a decision level for example, or right in that vicinity.

This has happened in glucose. We attempt to revise this by going to a scanning band throughout the total range of the analyte to get around that. So it's more objective in that regard.

DR. ADCOCK: Dr. Ng, I apologize, but I didn't catch your point. Could you reiterate what you said?

DR. NG: I think, I'm hoping it's what Dr. Kost picked up on that, the decision making is at these categorical limits. It's not in the continuum

everything you measure. So for me, the grave error occurs when you have a total discrepancy where one method gives a value that's not scary, but the other method gives a value where you're going to take action, and the action could have harm to the patient. So for hemoglobin, a hemoglobin less than 6, most people would probably want to do something. Hemoglobin greater than 16, they might want to do something. They might waffle in that range in the middle. So when I think about the mismatch, if one value gave you a hemoglobin of 10 and another method gave you a hemoglobin of 20, that 20 is in that LER range of greater than 16. And so that's not acceptable.

DR. ADCOCK: Thank you.

DR. NG: And just to round out, for platelets, I would say, I don't know, less than 20 and greater than 1.2 million. It's kind of where I would put my LERs.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: Well, I asked earlier if this concept of limits of erroneous results applied to moderate complexity or high complexity testing, and I think the answer was it applies only to waived testing, and I think what I'm hearing that we're

getting at is that the standards for allowable total error should be the same or more stringent for a waived method than for a lab method. And I think that this concept of LER is kind of quicksand for laboratory testing, and if we're going to apply the same standards for accuracy, to the waived method as we do for a moderately complex method, I don't see the point of having this limit for erroneous result. I think it's adding --

DR. GUTMAN: The nidus of this actually are the glucose papers, the Clark grid, and the Parks error grid, and the notion was that there would be values that were so extreme, they were just so -- I think, well, what Dr. Ng said, the values are just completely mis-signaled you because they were 180 degrees in the wrong direction. So I forget where that falls in the Clark error grid or the Parks error grid, but we stole that idea from them.

We don't apply that concept, but probably we do to glucose because we do -- but we don't in general worry in moderate complexity or high complexity labs about these kinds of outliers because of the notion that there is a regulatory environment which includes trained operators and proficiency testing, and so we're hoping that that regulatory

environment picks up these kinds of outliers.

Again, you can make recommendations. You can -- one recommendation would be that we, in fact, shouldn't have this category. I don't know, but we put this category in deliberately based on the notion that we really wanted to have some limit whereby if you fell outside of that and you did make the wrong choice, you know, there was an uncertainty about where to draw those lines, which is why we're bringing this issue to this group, and it seems to me that it's an earlier reflection in the course of the day, there's a question about whether either the line should be drawn, whether there's enough information to draw the lines.

So that's, that's an interesting different response than we expected, but I suppose that's a possible response.

DR. KULESZA: I actually was thinking that this LER is uniquely suited to waived devices because, as you said, in a hospital setting or in a more professional setting, that ridiculous value will either be repeated or will trigger an immediate action on the part of a moderate or high complexity lab that will curve and get to the bottom of the reason for why that value may be such an outlier.

For waived complexity, for the waived test, I think that this LER should be as Dr. Ng suggested, and I think that also it should be incorporated even more stringently down into the low values, comparing them with an alternative method. I think it would be technically difficult to get at the low numbers, but I think it should be there.

DR. SANDHAUS: You know, I'm getting confused actually by the discussion, and I think it might be helpful to have that diagram up on the screen if we could while we're discussing it. You know which figure I'm referring to.

DR. KOST: This one.

DR. SANDHAUS: Because I think we all might be saying similar things, but I know I'm getting confused.

I think what we're hearing, which was your suggestion, was that those limits of erroneous results be pushed towards the boundaries of the allowable total error so that they essentially become the same thing. In other words, and I'm saying the same thing but in a different way, which is let's get rid of the LER because it really is the allowable total error. We're making them more or less the same.

DR. NORBACK: In someplace in our reading, too, if the machine ever produces a result in the limit of erroneous result, well, then it can't be used in a waived setting. So I mean that's the definition. It can never produce that result, and that's why it needs to be challenged up front. If it ever produces a result like that, it can't be used.

DR. GUTMAN: Well, that actually was the intention. The advice we were looking was whether there were limits to define the outliers that we'd essentially sink a waiver. I'm a little bit confused. I'm actually not following. Are you suggesting that the limits be -- well --

DR. NORBACK: Eliminate the white part.

DR. GUTMAN: Well, I got that, but then you're suggesting that what was answered in the previous question, for example, in 6a, have dual purpose, that it be the allowable error and it also be the LER.

DR. ADCOCK: Dr. Kost.

DR. KOST: Well, I don't know how much forethought there was in drawing this particular drawing. It is in your guidance document. I take it this is out there since January, and I could be wrong because I haven't thought through this completely.

What you show here, which is a little different from up there, puts the absolute territory of no return bulging toward the sweet spot, if you will, of the measurement of the analyte. The parts that are heteroscedastic appear at the top, and then this flaky stuff that is always going to appear at the low end are not excluded by what you've drawn. So it's a very misleading diagram. Actually I think that perhaps, although I have no evidence base for this, that it should look like the opposite of what's been drawn here so as to satisfy this low-end problem that occurs with the CBC in particular.

DR. KONDRATOVICH: I think (off mic.)

DR. KOST: Yeah, what did you intend with this?

DR. KONDRATOVICH: Let me clarify. Here is really -- cartoon. It's not particularly related to any analyte, and only I would like to -- in some situations you are right. It can be very low. It's like can be like here. Only my picture I would like to show that sometimes it can be not symmetrical like in this cartoon. This can be larger. This can be example, a smaller area. For some region, maybe you need not have any erroneous results because like, for example, you have completely made the normal results

and in some situation maybe there are not set kind of like you can harm patient.

So my point is cartoon to show you basic idea, and you're right. You can have really very close to your allowable total error, but I would like to emphasize that, no, you cannot have absolutely the same because here would require like 95 percent, and inside of this white and light gray, you need to have like 100. So you need to have some room for 5 percent. So we're asking that how close you can be to this, and I understand you would like to be as close as possible, but, of course, not the same just because otherwise here is 95 and it's going to be 100.

DR. KOST: So it looks a lot like maybe you drew the idea for the Clark error grid --

DR. KONDRATOVICH: Yes, you're absolutely right.

DR. KOST: -- glucose analogy when, in fact, not yet published, it's in press. The second paper we have as technique shows that with a very accurate bedside, point-of-care glucose meter, there is nothing in any of those Clark zones.

DR. KONDRATOVICH: Yes.

DR. KOST: The Clark grid becomes obsolete

basically, and so the flip side of the coin that I would recommend in this consideration here is whatever would go out as a waived CBC device and so on, needs to be highly, highly accurate. I think that's what people are saying fundamentally and not just in the center of the measurement analyte range but at the ends as well.

DR. ADCOCK: Dr. Kulesza.

DR. KULESZA: Well, I don't know if I understand this correctly now because if you -- I am quite comfortable, I think, with the idea of the white being there, quite substantial. And in my mind at least, the zones of LER should not necessarily be drawn on the basis of analytical performance of the instrument. That's what the gray is for.

DR. KONDRATOVICH: Yes, you're absolutely right.

DR. KULESZA: But rather by the severity and consequences of the clinical scenarios, that the particular result entails. I think that that was the intent of the FDA if I understand it correctly to draw these results.

DR. KONDRATOVICH: You're absolutely right.

DR. KULESZA: And I think therefore that the shape of these curves and the placement of the

boundary is not necessarily related to the instrument and shouldn't necessarily be compressed towards the ATR but rather be dictated by what happens if we get this difference to the patient. I mean I don't know. If this is --

DR. KONDRATOVICH: Yes, you're absolutely right. You're absolutely right. There's more on the clinical concept. We have 95 percent observation here, and we don't like to have like, for example, formally 5 percent, 2.5 percent here. So we really need to have some zone for waiver test, that it's like prohibited zone.

DR. KULESZA: It's a red card.

DR. KONDRATOVICH: Yes, you're right.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: I'd like to, for a minute, sort of shift the discussion a little bit away from the actual statistic to what actually happens in real practice, and what's going to happen in real practice with the waived CBC is what happens with every other point-of-care test that's out there, and that is the doctor gets a result from the point-of-care instrument, and they don't like that result.

So now they redraw it, and they send it to the lab or maybe the point-of-care instrument, this

waived instrument, isn't going to give us a result or it's going to give a flagged result with a number, and then they redraw and they send it to the lab, and the number one question that comes back every single time with every single test is why doesn't my result match the lab test? Which one is right? And they don't have any understanding of which is the right result, and how can we tell them which one is right or there's no sense -- that we can't tell them which one is right in that particular instance.

And that's why the white zone there has got to be really, really small, because we're not just trying to reduce error or eliminate patient harm which, of course, we are trying to do, but we're trying to reduce discrepancies overall because that's what's creating a big problem with point-of-care testing is lack of understanding of variability in laboratory testing and the explanations for discrepancies.

Physicians do not expect discrepancies. They expect the white count to be the white count and the platelet count to be the platelet count every time exactly the same. So a platelet count of 10,000 by one instrument and 20,000 by another instrument to them is a discrepancy.

DR. KOST: Just a quick comment. In the use of the word discrepancy, we made the formal definition as discrepant values in the papers that are being published as those that affect decision making critically. So I would reemphasize that in the so-called challenged studies, we certainly have a case presented here today for challenging a potentially waived device with various types of specimens, so on and so forth, it's not enough to just challenge them. They have to be challenged around the decision levels. It has to be appropriately articulated as well. Thank you.

DR. ADCOCK: Please.

DR. BECKER: So I wonder if I understand this correctly, and if the Panel is intending to put this forward the way I understand it.

What I hear are two essentially re-definitions of that second boundary. The LER is defined in a particular manner now by that area which represents the zones in which one would surely expect patient harm to result from a discrepant result ending up in that area.

So rather than talking to the LER in that name, it seems to me that there really are two different concepts that have been brought forward

now. One is to redefine the LER in terms of saying that it is now a zone in which you can't perhaps rule out the possibility of there being some potential for patient harm there, you're simply beyond the ATE, and so it becomes essentially a no man's land, and you want all the no man's land to extend from just past the ATE out to infinity.

And then the second re-definition that I think I've just heard is that it becomes a zone that can be useful, not specifically from a clinical perspective, but from a discrepant avoidance perspective, which I think was the catch that Dr. Sandhaus was suggesting for, that you're looking at making the function of that area something different.

So LER as defined now has a function of marking the areas that would be likely to cause patient harm. Two other possible functions for that area, however you would name it, would be one of saying that it's just out past the ATE, still leaving some room for that 5 percent that has to somehow able to get outside there, but a large area where there might be essentially unknown results surely encompassing that the extremes, the possibility for patient harm, are not being confined to that.

And then the third, okay, second new definition would be simply a discrepant avoidance zone meant to be able to help suppress the likelihood that there would be discordances between the results as obtained from the waived device versus what would be obtained from the comparator device, assuming all comparators were alike.

DR. KOST: Well, and a fourth is you can use it to design the experimental model for challenges.

DR. BECKER: Okay. Thanks.

DR. ADCOCK: Dr. Bull.

DR. BULL: I had problems with this all day, and I'm still not sure I understand what its purpose is. But it seems to me that this is only going to be done at the time that the machine is being put through its paces prior to being acceptable as a waived test by the FDA. This isn't going to be done routinely. It's only going to be done once during the manufacturer's submission process, correct?

That being the case, it seems to me that all you're doing here is saying you don't want a machine in a waived setting that occasionally produces what I referred to as TRR, totally

ridiculous results.

What you've got here is, in your illustration, you've got the comparative method giving a value of, I don't know, 50 and the waived method giving a value of 800. Now, I can't conceive of a situation in which that could be related to other than a malfunction of the machine, and no manufacturer is actually going to submit a data set to you with any points in those ranges, for the obvious reason that you wouldn't accept it. So if what you're after is ensuring that manufacturers do not provide machines for the waived setting that give TRRs, then it seems to me that you should ask that. You should say that in a series of 360 tests, there should be no erratic results that can't possibly be a response to anything other than a machine malfunction in which one value on one parameter is 70 times the value on another parameter.

To define these regions in the way in which you've been talking about them doesn't seem to me to make any sense in terms of what I think you're after, which is that you don't get machines out there that occasionally misfire completely.

DR. ADCOCK: Would you like to approach the podium?

DR. KONDRATOVICH: (Off mic) this zone is really for the CLIA waiver study and notice that if somebody has at least one value among 360, we know that it's not suitable. There are some probabilities that this event happened because we see this in this clinical CLIA waiver study. So you're right. It's not like some zone which can be used in real clinical practice. It's more what kind of criteria we need to apply for device with the data from CLIA waiver study.

DR. BULL: Well, I can confidently predict that no manufacturer will ever submit a data set to you of any points there. Either they'll fix the machine and say, ah, we've now figured out why this machine occasionally glitches and gives us a totally ridiculous result and then start the study over again, or eliminate the data point because halfway through the study they discover that somebody pulled the plug out of the wall or something like that.

DR. KONDRATOVICH: Yes.

DR. BULL: And I think that's what you're getting after. I've been trying to wrap my mind around --

DR. KONDRATOVICH: You're absolutely right. So all the zone will be established before the

clinical study, and we're expecting that before they performance CLIA waiver study and they will see that, for example, in allowable total error zone, it's only 70 percent probably there are no need to submit data and also the same for LER, limits for erroneous results, is they have some point they have possibility not to submit, of course, because they definitely not pass.

DR. GUTMAN: But the purpose of having these numbers, if you buy into this concept, is that that gives the manufacturers a target to work for. In other words, they understand the rules of the game and will try to design, you're right, if they made a mistake, there probably wouldn't be high incentive to mail in a submission that's got all bad results, but they have, you know, they have a definition of what constitutes a result that is totally ridiculous as opposed to what constitutes a result which is not totally ridiculous.

DR. BULL: But statistically you could put a limit on what is a rational result and say anything outside of that will make the machine unacceptable for waived results, rather than going through the exercise of saying it has to fall in this.

You've got two methods, and you've got a

discrepancy in which one method is giving you 70 times the value of another. Now, nobody building a machine or no laboratory person would proceed further until they figured out --

DR. GUTMAN: All right. But what if it were 30 times but what if it was 5 times? In other words, we're trying to put -- maybe this is just --

DR. BULL: I would --

DR. GUTMAN: -- we're trying to put some kind of zone on that and, and contextually, you know, 70 times is easy. We figured out that 70 times is, probably for any analyzer, is unacceptable, and a 5 percent error is easy because it's probably --

DR. BULL: Quite acceptable.

DR. GUTMAN: Yes. Where between 5 percent and 70 percent do you draw the line? Or what principles do you use to draw the line?

DR. BULL: Well, I'm suggesting that you don't use areas on the map. You use a statistical assessment of the frequency with which you're going to get 5 standard deviation difference with your analytical methods or a 6 standard deviation difference, and once you've decided what that is, anything outside that makes the machine unacceptable, particularly if it occurs episodically.

DR. ADCOCK: Dr. Russek-Cohen, did you want to make a comment please?

DR. RUSSEK-COHEN: Yes, a couple of comments. Companies often do these studies without coming to the FDA first. Not everybody has the same notion of what the LER zone is. So some guidance where we could help companies along is better because sometimes there are points where one person's view is that should never occur, and another person says, well, it's fine with me, especially after I've invested in this large study. So the extent to which we need guidance and the fact of the matter is, is if you say a certain multiple, you know, like being off by 100 percent is unacceptable, it could translate into a region on a graph.

DR. BULL: I'd be happier seeing you do it statistically and then draw the map if you wish, but at least you could explain to the manufacturers that being off by 100 percent with your comparative method is going to invalidate the machine and they need to go back to the drawing board and design a better machine.

DR. RUSSEK-COHEN: Okay.

DR. NORBACK: May I comment?

DR. ADCOCK: Please, Dr. Norback.

DR. NORBACK: Okay. Thank you. It's been conceptually easier for me to think of this in absolute values, and if you would just indulge me for a minute. If we took the values of platelets from 10,000 up to 1,000,000, when somebody has a platelet count of 10,000, we could probably accept an error of 5,000. Now, if you want to make that 1,000 for discussion, that's fine, too, but just for the sake of discussion, let's say 5,000. And then if we got a value between 5,000 and 15,000, we're sort of in the same neighborhood, but if the value comes back of 30,000, to me that's not an acceptable error. That would be outside the limit.

Then when we go up the scale and we get up to 1,000,000 platelets, I think we'd like to have an error of maybe about 100,000, but if it was 400,000, this would be a problem because it would drop us down to, well, let's make it 500,000. If it dropped down to 500,000, that's a big difference between a 500,000 platelets and 1,000,000 platelets.

So that was just the way I approached these definitions and tried to make them clinically relevant, and you can do the same thing for every analyte. You could do that for neutrophils and lymphocytes and pick out what you want to be an

acceptable error, and I don't claim to know what the acceptable error is, but I think as a group we could come pretty close, and then you could also have a limit that's going to change the clinical decision as you go all the way up the scale, and here's where you pick out the points of clinical relevance.

There's a big area in the middle of platelets where 100,000 doesn't make any difference. You can have 100,000, 200,000, 300,000, 400,000 platelets and nobody particularly cares too much.

DR. KULESZA: There's another way. I mean, I am hearing the statistical approach to drawing the gray, I mean the black, the LER, I think would be often hiding other failures. Consider if, for example, you have different polyethylene for a PCR that we're running for Hep C, and they will draw out the DNA or absorb. Those are errors that can be caught presumably in a high complexity laboratory, but if something like this, and this will not be ridiculous type of, you know, somebody pulled the plug or there is an obviously machine fell on the floor, there might be sources of error that are somewhat unforeseen, but yet nevertheless they do occur. The waived machinery is completely unacceptable. It's out. And I don't think that

statistics in terms of drawing boundaries and drawing zones and percentages of an accurate result is the appropriate way to go about it.

DR. NORBACK: It should be empirical.

DR. KULESZA: Yes, absolutely. And it should be particular for each analyte just like you said because the clinical consequence is driving it rather than the analytical performance of the machine and, yes, I can accept, you know, pulling plugs and stuff, but I hope that the manufacturers are at least not that cagey, I think is the right word, you know. If something like that occurs, the FDA has the right to know line data, step by step, each bar coded specimen as it comes off of the machine.

DR. ADCOCK: Dr. Sandhaus.

DR. SANDHAUS: I'm reluctant to make this comment, but I guess I want to reiterate a point. You know, I really agree with what Dr. Norback said about, you know, the examples you gave for acceptable errors and platelet counts, and you or I wouldn't be concerned if we saw a platelet count that was 250,000 and whether it was 300,000. It wouldn't bother us. Nor would it bother a physician, but what happens with point-of-care testing is that you have intermediaries, your testing personnel, who are

untrained or minimally trained, and to them a discrepancy of 250,000 to 300,000 is a big discrepancy. They don't understand the clinical significance or lack of significance of that difference, and this creates a lot of confusion in the testing environment.

And sometimes difference such as this get communicated to patients in a way that can create confusion for the patient, and some specific examples that come to mind, where I've seen this kind of confusion, with other testing, not with CBC testing, but for example, a cardiac perfusionist in open heart surgery complained at our institution about discrepancies in blood gas results between the point-of-care instrument and the lab instrument, and the particular complaint was that the pHs weren't matching, and the patient result that was cited was a pH of 7.29 and a pH of 7.31. Now, people who understand laboratory medicine would not see that as a discrepancy, but in the point-of-care setting, this becomes problematic.

So these platelet counts that you cited as examples, while I agree with you absolutely, on the cutoffs that you were suggesting, in the real world, in practice, those things get translated into

something else, and a hemoglobin that is .1 gram per deciliter above or below the reference range could be communicated to a patient as, oh, your result is abnormal, you're anemic when, in fact, they aren't, and these things can lead to additional testing, to other misconceptions, and who knows what.

DR. KOST: I suppose I'm being overly cynical, but what we're hearing here is that in most esteemed evaluations of Panel opinions and guideline documents, they're always put at the bottom of the stack as having the least value, whereas evidenced-based studies and what have you have the greatest value, particularly if they're done in a controlled fashion, so on and so forth.

So frankly, I feel, although I don't agree with anything that's been said by the Panel, seem to be very shrewd opinions, but I fail to see how in realistic consideration by the FDA of potential waived devices you'll be able to set these guidelines preemptively and proactively. I think there has to be more actual evidence come forward.

And a even bolder suggestion might be that point-of-care testing has really come of age now. I mean, we're hearing the good and bad of it today, and we have 100 or whatever waived tests, so on and so

forth. When will we have an independent arbitrator to actually validate these devices? When will we have, I don't care who does it, but rather than industry, once industry is all primed and ready to go, why not have an independent body that actually does the validation of the accuracy of the devices and get around a lot of the pre-manipulation of the data. You know, you don't want to be totally harsh on industry in predicting that they will skirt around all of these funny zones that are drawn.

Actually in most data sets, the reality is that industry for one reason or another going out to multiple sites will collect a lot of data in the middle because that's where the data points lie. It's very difficult to get the highs and the lows. It's very difficult, particularly, in fact, I can't picture how we could do that in a waived setting because those that are screening tests, and a lot of those patients are going to be -- normal, they're going to produce a lot of measurement in the sweet spot of that graph up there.

DR. ADCOCK: Additional comments?

(No response.)

DR. ADCOCK: At this time then, if I can summarize the Panel's opinion, in regard to

determining how the LERs should be obtained, or determined for each of these analytes, there was significant discussion and perhaps no real consensus. There's some thought that perhaps the LER should be redefined, that perhaps we should look at clinically relevant zones and, for each of the ranges that we're measuring, determine when clinical decision-making occurs, and if results should vary in a significant manner, to change clinical decision making and that would be different along each of the analytes and along the range.

And then I would also propose that perhaps Dr. Becker's synopsis be taken to heart, that perhaps the LER should become a discrepant, avoidance zone or should be defined as one where we would avoid discrepancies.

Would there be any additional summaries? I don't know that any consensus can be drawn.

DR. GUTMAN: Thank you.

DR. ADCOCK: Should we move onto number 7 or --

MS. BAUTISTA: C.

DR. ADCOCK: 6c, pardon me.

MS. BAUTISTA: This is 6c. In the CLIA 88 regulation, there are no ATE criteria, either as

percentages or as absolute counts, for WBC differentials, and consensus recommendations on ATE are not found elsewhere. An example of recommendations for maximum differences between duplicate measurements from the CDC NHANES program is: neutrophils 0.4x10 to the 9th; lymphocytes 0.2x 10 to the 9th; monocytes 0.2x10 to the 9th; eosinophils .02x10 to the 9th; basophils 0.2x10 to the 9th, and those are in liters.

You may wish to define ATE limits that vary by ranges within analytes, i.e., across cut-off values that drive various medical decisions. For purposes of discussion, we suggest analyte-specific ranges in the following two slides. FDA requests ATE recommendations for three-part and five-part differential counts.

This is 6c continued. To assure clinically relevant performance, what ATE do you recommend for three-part differentials and in the following slide, five-part differentials? You may specify limits as a percentage or in absolute numerical counts.

And the next slide also for continuation. Please recommend ATE here for five-part differential counts in which granulocytes are further differentiated as neutrophils, eosinophils, and

basophils. You may specify limits as a percentage or in absolute numerical counts.

DR. ADCOCK: Thank you. So it seems as though this is leading based on what we've already been talking about. I'd like to know if the committee feels that at this time we can suggest ranges?

DR. SANDHAUS: They should be the same as they are for current analyzers, automated analyzers in the laboratory.

DR. ADCOCK: So Dr. Sandhaus suggested that the ranges we propose be the same as for already FDA approved analyzers that are in the laboratories. Yes, Dr. Kost.

DR. KOST: A lot of what we do in the lab is based on peer performance, peer review performance based on proficiency testing, and one could make a case for actually we need some absolute accuracy standards because perhaps the proficiency testing story is not the whole story, and I think the case will come up in the next few years for point-of-care testing as well, that we do need some absolute accuracy standards, and those standards would allow one to determine such ATE when we actually see how the instruments can do.

Now, my personal opinion is while I could give some guesses at this, I would only strike at a few of the high points, such as granulocytes that are 0500, 600, so on, the tolerance for error there has to be extremely low because the critical limits, the critical values that are used for notification of same are fairly tight when you look at means, and the FDA could consider some of the critical limit means and standard deviations that are published in the JAMA paper and also Journal Pediatrics some years ago. It's outdated, but it's still reflects some of the key decision levels, the actionable levels.

As you know, the Joint Commission has put additional weight this year, the 2009 patient safety goals includes proper notification and documentation of critical results, and so these should not be omitted in the consideration of approval of any waived device, and this is a triple-edged sword, if you will, because if the error is made, it's going to hurt the hospital, the patient, and industry as well. They'll all be in the lawsuit.

DR. ADCOCK: Additional comments? Dr. Ng.

DR. NG: Well, I was just going to comment on the reference intervals. I think we heard earlier today that manufacturers typically do not provide

reference intervals. They give you sort of a broad stroke, but then you have to customize it for your own patient population. So that's why I'm having a lot of ambivalence about making any suggestions of reference range, and if I can't make a suggestion on a reference range, I can't even begin to think about what the ATE should be for each of those reference intervals.

DR. ADCOCK: Dr. Norback.

DR. NORBACK: I did look at allowable ranges on one of the analytical commercial instruments, and for neutrophils in the midrange, I think the allowable error would be 400. I think that's too high for neutrophils, and I think we can do better, and I think we would want to consider more stringent controls if we were considering a waived instrument. And I guess what I'm thinking is that it makes a difference if somebody has a neutrophil count of 500 or 1,000 or 1500 or getting into the normal range, and if we allow an error of 400, you know, we're just not distinguishing between these important levels.

So I would just say that I think if we're considering waived instruments or use of instruments in a waived setting, we would want more stringent

total errors. It would have to be narrower, and they're really pretty generous as they exist in the laboratory right now.

DR. KOST: Dr. Norback's point is very much to the point, the point of care, because there is litigation now over these low neutrophil counts, and the issue is, is the doc getting the information, et cetera, particularly important in the clinical setting of sepsis and incipient sepsis where the patient is subject to potential sudden death, as it were, from the flood of pathogens and whatever happens there.

DR. ADCOCK: Additional comments from the Panel?

DR. SANDHAUS: I think this is very interesting that there seems to be a trend here of recommending that the waived instrument, that the requirements for accuracy be more stringent than for the laboratory instrument, and I think that's very interesting because if such an instrument really does become available, then that would be the instrument I would want in my laboratory.

DR. ADCOCK: Then to summarize, Dr. Gutman, I believe that the Panel generally feels that the accuracy standards as they are currently available

would be the minimum and that the Panel would recommend perhaps more stringent numbers.

DR. GUTMAN: Yeah, if members of the Panel do have references that would be relevant to this or materials that would be relevant to this, if you would send it to us post-Panel, we would be very grateful. Our 510(k) process is a colorful process that provides glimpses into products but may not be as reassuring as a benchmark we might like. So any help from the Panel in terms of informing us about what the state of the art should be or is would be useful.

DR. KOST: It's an interesting observation in the last year or so that industry, of course, has done this for a while, but a lot of other professionals, clinical professionals are drifting away from the laboratory when it comes to point-of-care testing. In a way, they don't consider the laboratory as relevant as they used to consider because a lot of decision making is made on the result at the point of care.

So I would personally like to inspire the FDA to lead the way on this. In fact, the observation of Dr. Sandhaus is particularly astute in sensing what's going on here. The point-of-care

testing really needs to be the definitive test of the future. It's going to be out there. And so there can be no compromise on accuracy, and that's what we need, I think. Personally I think the -- decades seen in the next 10 years, the FDA really needs to charge forward in that regard.

DR. ADCOCK: Dr. Wang.

DR. WANG: In the review article, Dr. Russek-Cohen referred to earlier, they actually provided allowable total error for the CBC as well, but they're in percentage, not in absolute values.

DR. RUSSEK-COHEN: (Off mic.)

DR. ADCOCK: Would you be kind enough to approach the microphone.

DR. RUSSEK-COHEN: The article implied that -- when Dr. Kondratovich talked about this idea of considering biological variation and analytical variation, it used a fairly high criteria for analytical variation, that it would meet up with about half the biological. So, in fact, the ATE may be higher and might be desirable, and so we weren't necessarily saying the way they've gone about calculating the ATE would be appropriate. And then there's also the issue that they used the uniform percentage throughout the whole range and that may

not be clinically the most sensible thing to do.

DR. ADCOCK: Dr. Ng.

DR. NG: Just a tangential thing to throw out when I look at these white cell parameters. There are a couple entities where the absolutely count is diagnostic. So I'm thinking the precision around those diagnostic points would be important to demonstrate, and I'm thinking of lymphocytes of I believe it's 10,000 or greater for CLL, chronic lymphocytic leukemia, primary eosinophilic syndrome, hypereosinophilia. I can't remember the number, but there's some number that makes a diagnosis.

And then, of course, to reemphasize the neutrophils, the absent neutrophil count of 500, a very critical limit to assure accuracy.

DR. ADCOCK: Would the Panel like to add any additional comment at this time? Please, Dr. Bull.

DR. BULL: We've talked a fair bit about point-of-care testing, and we've talked about waived testing, and there has been, as near as I can determine, the implicit assumption that point-of-care testing and waived testing are similar.

I would have thought, however, that they were really in some sense quite different because

point-of-care testing has access to trained personnel and professionals for interpretation of curious results. I'd like to hear from those who are experts in point-of-care testing, how they see the relationship in their realm of responsibility to waived testing, what are the similarities and differences and what might be useful to the FDA as it considers waived testing.

DR. KOST: There's a White Paper, as it were, published in Chest where the critical care physician, laboratorians, and so on, agreed to a uniform definition of point-of-care testing as being any testing at or near the site of patient care. So waived and point of care in that definition would be synonyms. They're synonymous. There's really no distinction. Push comes to shove when you get over into other countries, and you see that by model, if not in reality, what the FDA has deemed waived in the end is used for all kinds of applications, and so, you know, should the net result here be to waive a CBC device or even hemoglobin or hematocrit, it's going to be used for transfusion decisions in another country, I guarantee.

DR. SANDHAUS: In this country.

DR. KOST: Well, this country, too. I

don't want to see it, but the reality is yes.

So personally I think we should recommend sticking to the definition of point-of-care testing as diagnostic testing at or near the site of patient care. The word waived does not appear as part of that definition.

DR. BULL: I suspected that that's what we were talking about, but it's nice to have it out, laid out on the table for us.

DR. KOST: Yeah, nobody exactly knows where the term of point-of-care testing came from. We ourselves take credit for it in our glory moments at UCD Medical Center, but to prevent disaster, I tried to trademark that term, and it was turned down because, of course, the usual astute documentation of the Patent Trademark Office is being part of it, it's an English word now. It appears in dictionaries and everything else, and that's the kind of definition that it's used in.

DR. SANDHAUS: I think it's important to be clear about what we're talking about and people might make different assumptions. So I'm glad you asked that question. You know, obviously you can do a waived method in the laboratory, and you can use a waived method at the point of care where it's being

done by non-laboratory personnel, and that's the setting I think that's more concerning, and that's where there's obviously less control over how the test is used, but when we use waived methods in our laboratory, it's subject to the same standards as all the other laboratory tests that are done in the laboratory.

DR. KOST: And the reason for that, of course, is the Joint Commission insists on that. In the hospital setting, we don't have waived testing. It's accepted from all of above rules. I mean, we have to fulfill the Joint Commission and other accreditation bodies' expectations for quality control, training, competency, et cetera.

DR. ADCOCK: Additional comments at this time?

(No response.)

DR. ADCOCK: Then at this time, I would like to very much thank the Panel --

UNIDENTIFIED SPEAKER: We have one more.

DR. ADCOCK: Oh, sorry. We do have additional questions. Pardon me. I do believe we have an additional question.

MS. BAUTISTA: Okay. This is 6d. Limits of erroneous results represent results for which the

error is large enough to represent harm to the patient. For each analyte, what it the maximum error that would not endanger a patient's health?

DR. GUTMAN: I would actually suggest that we defer this in light of the discussion on the previous --

DR. ADCOCK: Thank you. I concur.

So Number 7 please.

MS. BAUTISTA: Number 7, Quality Control. What frequency of quality control should be performed for these analytes in the waived setting? With what circumstances or events should additional QC measurements be performed, such as every new log, every new operator?

DR. ADCOCK: Comments?

MS. RICE: It should be performed daily with every new operator, with every change of reagents, and if like Dr. Ng talked about, if you drop the instrument or something happens to the instrument, or you get a questionable result.

DR. ADCOCK: So I just didn't catch the very first thing you said, with --

MS. RICE: Daily.

DR. ADCOCK: Daily.

MS. RICE: Change of operator, change of

reagent lot numbers, let's see. My mind's gone blank.

DR. ADCOCK: Change of instrumentation.

DR. RICE: Change of instrumentation, if anything happens to that instrument where you have to change even a light bulb, that I don't think it would quality it for a waived instrument, you should do QC on it, and I know a lot of waived instruments now have internal quality control, electronic quality control, and if a CBC analyzer would have that, I think you should also have to do the external daily. Do both internal and external daily.

DR. ADCOCK: And then any recommendations for should the QC be out?

MS. RICE: Laboratory standards but probably not, no. Because you would have untrained operators who don't understand Westgard rules. So I think you should recommend that the QC has to be in.

MR. BRACCO: I would like to add that it has to have two levels --

MS. RICE: Yes.

MR. BRACCO: -- medium and high, at least two levels.

MS. RICE: I agree.

DR. KULESZA: I would imagine that most of

these -- I mean my biggest concern with waived testing would be that the machine locks out and doesn't allow any further testing to be performed if the QC test has failed and that the QC test, the frequency of it, I don't know that I can have an opinion. It presumably could be done per number of tests performed, but it would be technological argument rather than a daily or even monthly. I don't know what manufacturers can do. Maybe there are machines that can be QC'ed every six months like the -- I mean, I don't believe it, but the interval is not something I would be comfortable on commenting without knowing the technological aspects of the device.

However, the machines that we currently have in the labs can defeat controls, i.e., QC is not passed. The machine will produce a result. That would be totally unacceptable in a waived setting I would imagine.

MS. RICE: I have seen glucose analyzers where they have overridden the lockout.

DR. KULESZA: Right. So I would like to have a device that the lockout cannot be overridden period. It shuts off. There's no electron going from one place to another, done. I think that that

would be the only acceptable machine to me in a waived setting.

And I think also that the control cartridges should be produced or the two level controls in such a manner that they would be stable and have a little bit more of a different process perhaps than the internal analyzers that we use, and we can create controls in the lab. It's not a big problem for us to draw blood and re-QC or do delta checks or so forth.

I think this waived machine should have QC packets that are designed in such a way that they can take a little bit more abuse and should be tested as part of the challenge to the machine, flex testing or what have you, as the machine is being presented to the FDA for approval.

DR. NG: But I have a caveat on the QC. I would insist that however they generate whatever the QC pathway, it must mimic the patient specimen flow. So that application point is so critical in getting the correct result.

I would also ask that if QC is being done, that if somebody decides to go to the equivalent QC process, that the same requirements hold forth between the last successful QC event and the

subsequent failed QC event, that somebody has to review the importance and the clinical relevance of every result generated in that interval when the QC presumably was out.

DR. AZIZ: One thing that we can also suggest is the availability of peer review between analyzers, and that will give credibility for that instrument.

DR. ADCOCK: I'm sorry. Can you repeat that, Doctor?

DR. AZIZ: A peer review, so I mean I can compare my -- or my meter that I'm using with his and theirs and everybody else.

DR. ADCOCK: So you're proposing in addition to QC, that there be proficiency testing?

DR. AZIZ: No, not necessarily proficiency testing, but a peer review. Basically like I submit monthly reports of my QC and compare it with other labs, to see how that lot number compared to the other one.

DR. NG: So it's like the Bio-Rad or the Abbott programs?

DR. AZIZ: Yeah.

DR. NG: All the labs on that same lot send into a central database and you see how you compare.

I agree.

DR. ADCOCK: A program perhaps by the manufacturer?

DR. NG: Or third party.

DR. KOST: I think the last time I looked at package insert for a waived test, it either didn't mention QC or it said, well, throw it out the window and you maybe might consider possibly checking it sometime or something to that effect. So am I wrong about the definition of waived testing? I think it was said earlier today that there's really no QC requirement --

DR. GUTMAN: No, that's actually wrong.

DR. KOST: I guess you guys have to -- that's wrong.

DR. GUTMAN: That's wrong.

DR. KOST: Tell me what is the rule please that you're operating under then in regard to --

DR. GUTMAN: No, we do have recommended QC intervals usually tend to be with each lot when their reagent changed, when their instrument changes. We do not have one that explicitly requires daily QC. So there's a maximum. I forget -- there's a maximum size on lots, 25. So that you can't run more than 25 samples without a new QC. So it's, it's a

miscommunication if you believe there's no QC requirements. There actually are.

DR. KOST: Is this part of the package insert or --

DR. GUTMAN: Yes, it should be. So if you've identified one where they've changed, you need to let us know so we can find out why they've decided to arbitrarily drop the QC or, of course, we could make an error.

DR. KOST: And then the flip side of the coin is to pose that we have a new technology that has no lots identified, the ideal technology. Then what would you say about QC?

DR. GUTMAN: Good question. We haven't run into anything that doesn't have lots yet, but we would probably look for some alternative frequency, every certain number of tests I suppose.

DR. ADCOCK: Dr. Bull.

DR. BULL: Further to this discussion, it's my understanding that the QC would be specified in the manufacturer's recommendations for which 30 percent of the laboratories are lacking. And since nobody checks to see that the QC is done, I'm not clear on how you would actually find out unless you designed the machine that had to have a cassette in a

waived setting that after a certain number of specimens, it would quit running unless you fed it a QC sample. I don't see that we have a mechanism other than advising, which I guess you do now, but you don't have any way of checking to see if the follow the advice, but a QC program in which there's no way of checking to see if it's being implemented is useless.

So for a waived machine, it seems to me that the machines themselves are going to have to be -- if nobody's going to check or train or do anything, the machines themselves will have to shut down if the QC program is not required in order to keep them operating.

DR. NG: Am I the only one who has glucose meters. If you don't run two levels every 24 hours, you shut down? -- shut down in 24, so if it is shut -- that can be filled in --

The leukocyte S trace and the nitrite, that's two levels every 24 hours. That's a manual thing you've got to do. So there are a lot of waived tests out there that do have QC requirements. But the instruments you can control. That I like.

DR. BULL: Yeah, well, I'm just suggesting that one of the requirements that we recommend as a

Panel is that the instruments do shut down unless the appropriate QC material is provided to it and that the material gives the expected results.

Well, what are you going to do with this machine shutting down now for the next 24, 48, 96 hours? Until the manufacturer's representative gets out there, there's going to be no testing available at all. Is that not going to harm patient care?

DR. AZIZ: Presumably better than wrong testing.

DR. SANDHAUS: That's why the salesmen sell you two. That's experience from the field.

DR. ADCOCK: Any additional comments from the Panel?

DR. SANDHAUS: Maybe one.

DR. ADCOCK: Yes.

DR. SANDHAUS: This is just some general comments on QC, again some evidence based. I think that QC is one of the most widely misunderstood concepts in laboratory medicine outside of the laboratory. And in the laboratory, I mean I don't know what percentage of our testing is actually QC, but technologists live and breathe QC, and it's part of the culture of the laboratory. It is not part of the culture in clinical medicine now, and it's very

misunderstood. The types of misunderstandings that I can find on a daily basis as Director of Point-of-Care Testing in a hospital are the notion that QC can be repeated, should be repeated until it's in. Okay. And this is, of course, why we have QC lockout. This is why QC lockout was invented which is a good thing.

But another very prevalent notion is that the testing personnel don't have time to do QC. In a laboratory, of course, we wouldn't accept that notion. QC is, it's an attitude, I like to say. It's a frame of mind, and I think my point of view, when I'm confronted with that reaction from testing personnel, is that if they don't have time to do the QC, then they really don't have time to do the testing.

But what we find with a lot of manufacturers is that sometimes the QC is, if it's external QC, it's more difficult for the testing personnel to perform than the actual patient test. They might have to reconstitute some QC material or the QC, for example, with the troponin instrument that we have, well, it takes 14 minutes to run the QC, and if they have to run two levels of QC, you're talking about a half an hour of time, and their reaction is, well, we don't have time to do that.

So all of these issues that are related not just to, you know, the reliability of the QC and so on, but actually performing it, the actual logistics of getting it done, in the waived testing setting, those are problematic issues that need to be addressed. And the manufacturers' sales reps do not address that.

DR. ADCOCK: Dr. Kost.

DR. KOST: I think that someone once told me that quality control is intended to check the performance of the operator as well. And I guess in our program probably most other point-of-care programs in the hospital setting, we can't possibly do that with every operator. So the implication for waived testing is that technology should probably have this on board, as Dr. Bull suggested, and specifically not just equivalent or electronic quality control on board, but for this complicated testing that we're talking about today, probably some kind of wet concept intrinsic to the instrument if this is possible.

DR. SANDHAUS: Well, could I respond? The problem with on board QC though is that it isn't QC'ing the entire testing process. It's only QC'ing the analytical phase, and that again, then the

testing personnel feel even, you know, less responsibility for the testing.

Another aspect of the QC is some of the regulatory agencies, at least one that I know of, requires that the QC be rotated among the testing personnel, and what you run into over and over again in the testing situations is that they've designated one person to do the QC daily, and that's how they've solved the problem, and then we have to inform them that that's not satisfactory, and again that's a problem because you may have hundreds of operators who are performing testing infrequently. So it's very difficult to QC your entire testing process.

DR. ADCOCK: Any additional comments?

(No response.)

DR. ADCOCK: In summary, the Panel generally feels that QC is a important component of the testing and that it be offered at multiple levels in a manner to mimic patient samples with a QC lockout option of the instrument or portion of the instrument -- function of the instrument.

Is that sufficient?

DR. GUTMAN: Yes.

DR. ADCOCK: Have we answered all of the questions now?

MS. BAUTISTA: Yes.

DR. ADCOCK: All right. Well, then at this time I would very much like to thank the Panel for their attendance and participation today, the FDA, the speakers, including our guest speaker today, and the public speakers earlier this morning.

Dr. Gutman, is there anything that you would like to say?

DR. GUTMAN: No. I'd like to reiterate, to thank the Panel. I'd like to thank you in particular for doing such a wonderful job at keeping us moving on very complex issues. I thank my colleagues at FDA, at CMS and CDC for helping put this together. So thanks you all.

DR. ADCOCK: At this time, I would like to adjourn the meeting of the Hematology and Pathology Devices Panel.

(Whereupon, at 4:49 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

HEMATOLOGY AND PATHOLOGY DEVICES PANEL

July 18, 2008

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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Dominick Quattrochiocchi

Official Reporter