SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

HEMATOLOGY AND PATHOLOGY DEVICES PANEL

July 18, 2008

Hilton Washington DC North
Gaithersburg, MD

Attendees:

Chairperson
Dorothy M. Adcock, M.D.
Esoterix Laboratory
Englewood, CO

Voting Members
Piotr Kulesza, M.D., Ph.D.
University of Alabama at Birmingham
Birmingham, AL

Helen H. Wang, M.D., DR.P.
Beth Israel Deaconess Medical Center
Boston, MA

Temporary Voting Members
Brian S. Bull, M.D.
Loma Linda Univ. School of Medicine
Loma Linda, CA

John A. Koepke, M.D.
Duke University Medical Center
Durham, NC

Gerald J. Kost, M.D., Ph.D.
University of California School of Medicine
Davis, CA

Valerie Ng, Ph.D., M.D.
Highland General Hospital
Oakland, CA

Diane H. Norback, M.D., Ph.D.
University of Wisconsin Hospital
Madison, WI

Anne S. Rice, MT(ASCP)
Centers for Disease Control and Prevention
Atlanta, GA

Linda M. Sandhaus, M.S., M.D.
Case Western Reserve University School of Medicine
Cleveland, OH

Consumer Representative
Hassan Aziz, Ph.D.
Armstrong Atlantic State University
Savannah, GA

Industry Representative
Dan Bracco
Oxford Immunotech
Marlborough, MA

Executive Secretary
Louise E. Magruder
CDRH
Food and Drug Administration
Rockville, MD

CALL TO ORDER

Panel Chairperson Dorothy M. Adcock, M.D., called the meeting to order at 8:00 a.m. and introduced Ms. Magruder, the Executive Secretary for the Hematology and Pathology Devices Panel, for introductory remarks.

OPENING REMARKS - INTRODUCTION

Executive Secretary Louise E. Magruder read the FDA Conflict of Interest Disclosure Statement. She reported that conflict of interest waivers had been issued, in accordance with 18 U.S.C. Section 208(b)(3) and Paragraph 712 of the FD&C Act, to Chairperson Adcock; that theses waivers address a speaking interest with one of the firms at issue; that she received less than $5,001; that this involvement was unrelated to the meeting agenda; and that the waivers allowed her to participate fully in the deliberations. She added that the FDA's reason for issuing the waivers are described in the waiver documents which can be found at the FDA's website (www.fda.gov) and explained how copies of the waivers could be attained and that a copy was available for review.

After introducing Dan Bracco as the industry representative, she then noted the conditions of exclusion for participants and that the Panel should be advised of any financial relationships participants may have with any firms at issue. She made general announcements concerning availability of transcripts and purchasing videos and indicated that Karen Riley was the press contact for the meeting.

She then indicated that the FDA would be seeking the Panel's input on whether CBC with differential counter is a reasonable candidate for waiver and that deliberations of the committee will be presented at the September CLIAC meeting.

She then concluded that following the open public hearing, the FDA would be making four presentations, that CMS would provide perspectives from the CLIA (Clinical Laboratory Improvement Amendments) program, and that the rest of the day would be devoted to Panel discussions.

Chairperson Adcock then advised that the Panel would be discussing and making recommendations on issues relevant to the potential for CLIA waiver of automated differential cell counter and that the Panel discussion would include pre-analytical, analytical, and post-analytical issues associated with performing the automated hematology complete blood counts (CBC) and differentials in a waived setting.

She then asked the Panel members and FDA staff to introduce themselves.

OPEN PUBLIC HEARING

Chairperson Adcock proceeded with the open public hearing, advising that public attendees are given the opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

She went on to ask, in order to ensure transparency, that all public hearing speakers advise the Committee of any financial relationships with any company or group that may be affected by the topic of the meeting or if no such relationships exist.

She directed all public speakers to approach the podium to answer questions, if addressed by the Panel, and then announced that there were three requests to speak

Ray Osmond was the first to speak. He indicated that as a medical technologist for almost 50 years and a laboratory consultant for 10, he has firsthand knowledge of the users of this equipment. He related that his laboratory personnel are having enough difficulties with the present waived testing.

He gave a brief history of CLIA, stating that it was signed into law because of the high incidence or perceived high incidence of laboratory errors.

He explained that this law was divided into three categories: high complexity, marked complexity, and waived tests, which employ methodologies that are so simple and accurate that even if done incorrectly would cause no harm. He added that the waived test category requires no personnel standards, minimal or no quality control practices, no expert or proficiency testing, and minimal inspections from outside agencies.

He stated that the Certificate of Waiver requires a license, a director, training of personnel, a procedure manual, and the requirement to follow the manufacturer's directions. He pointed out that these directions do not indicate requirements to perform quality control and that there are now many waived tests already on the market that do not require quality control.

He went on to express his opinion that this issue is not about patient care but that it is about money. He pointed out that this is not new technology, having been around for the past 20 years; the cell counter for 50.

He stated that the approval of this request would increase the stock pay of the hematology companies; that it will have a definite impact in physician errors due to new and untrained people using the equipment; and that the present users of hematology equipment will opt out of proficiency testing and of being inspected by outside agencies. He added that this will have an adverse effect on the quality, accuracy, and reliability that is now in place.

He presented three studies that speak to the user and asked that before a decision is made, the FDA should be asked to prove simple and hazardous analysis and also to prove that they have studies in place.

He then went on to express his concerns about changes being made in required quality control and of no quality control being performed in

physicians' offices and his hope that the Panel recommend that they not go forward with the proposal on the application of the CDC as a waived test. He urged that the Panel recommend to the FDA that a panel of stakeholders be convened for further examination of this issue.

He concluded by stating his view that the FDA is biased in favor of big business, that the playing field should be leveled and patient safety should be the utmost concern of the FDA and the Panel.

L. Michael Snyder, Chairman of the Department of Hospital Labs at the UMass Memorial Medical Center in Worcester, Massachusetts, was the second speaker. He began by stating that he is a practicing hematologist and addressed the importance of having a test available immediately in order to maintain good quality and ensure adequate decision making as to the use of antibiotics by patients and clinicians.

He presented that one of the major problems in public health is the emergence of resistant anti-bacteria which has caused significant morbidity, mortality, and cost and that a clear waived test will offer physicians in remote sites the ability to make informed decisions.

He then spoke of a study that his department did, as a result in looking for handheld devices, with a company called Chempaq, comparing their product with the LH 750, stating that the results were published in the Clinical Chem Lab in March of 2008.

He then indicated that they are now performing the same type of test using lay personnel, clerks, secretaries, et cetera, that they are finding very similar test results and are very optimistic about this.

He discussed the risks of tests, for example, error resulting from pre-analytic data; missing, freezing and mislabeling of samples; and short draws, among others. He stated that he feels the device is simple to use and also stressed the importance of the ability of clinicians in remote areas to make informed decisions as to the appropriateness of the use of antibiotics. He talked about the need for having a device which flags abnormal cells and which will shut off if a short draw should occur.

He concluded by stressing the importance of a Point-of-Care test that is accurate and easy to do and of the positive impact this will have on patient care.

Paul Rust, Vice President of Quest Diagnostics and Managing Director of HemoCue, was the third speaker.

He related that his involvement in the in vitro diagnostic business began in 1970 and he has a unique perspective due to his many years' experience in the business. Having also managed laboratories in New York and California, he has experience with the pre-analytic, analytic, and post-analytic processes.

He spoke of the possibility of giving physicians a choice between overnight testing and Point-of-Care testing and the different needs of patients.

He pointed out, as did Dr. Snyder, the importance of physicians and patients being able to make important decisions quickly in remote locations or locations where test results are not readily available.

He spoke of his company's white blood cell analyzer that was designed with the CLIA waiver guidelines in place, a one-parameter analyzer with 30 error codes built into the software to flag things that go wrong so that a medical technologist is not required to run the system.

He went on to relate the findings of his company's pediatrician evaluator in using the device. He stated that the company believes it is the right technology available to pediatricians to dramatically reduce the use of antibiotics.

He concluded by encouraging the Panel to support the notion of selecting the appropriate products for waiver and encouraged the industry to develop products that are designed to meet the stringent requirements for a CLIA-waived lab.

PANEL QUESTIONS FOR OPEN PUBLIC HEARING SPEAKERS

During a brief question and answer session, **Dr. Bull** questioned Mr. Osmond as to why he believed the instance of quality control would decrease if a waived test for CBC were to be granted. The question was followed by discussion from the Panel members.

FDA INTRODUCTION

Josephine Bautista, M.S., MT(ASCP), Associate Director for Hematology Devices in the Office of In Vitro Diagnostic Devices, began by giving an overview of the FDA presentation.

She stated that the purpose of the meeting was to discuss if automated differential or automated hematology devices with or without differential cell counters can be waived. She added that the Panel is an issues panel and that CBCs, parts of CBCs, differentials (three part and five part) would be discussed, but that no particular device would be.

She went on to explain the importance of setting up parameters on the waiver issue and pointed out that there is no specific performance set for these kinds of devices. She spoke of the risks and benefits associated with these devices and of the many questions and issues surrounding the implementation of waiving these types of devices. Ms. Bautista then raised the issue of how questionable results are to be validated because in the waived setting there are no flags, histograms, indices, and other parameters to assist in making decisions as to the accuracy of these results.

She also brought to the Panel's attention the issues of what are the acceptable risk levels in association with these types of devices and of the ability of untrained users to interpret and analyze these types of results and asked for the Panel's input on these questions.

Ms. Bautista finished the overview by explaining the two parts of the presentation and then introduced the speakers.

FDA SPEAKERS

Carol C. Benson, M.A., Associate Director, Division of Chemistry and Toxicology Devices, began by advising the Panel that she would be talking about CLIA waiver in general terms as an introduction to CLIA waiver and that she would be discussing its impact and the concepts of a test system for CLIA-waived categorization.

She explained that CLIA-waived devices are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that (A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible or (B) pose no unreasonable risk of harm to the patient if performed incorrectly. She pointed out that there is an "or" between (A) and (B), not an "and."

She then went on to discuss the impact of CLIA waived test systems and the benefits for patients because the tests and results could be present at the time of the visit with their physician. Also, that it would help with the personnel shortage of trained laboratory workers because waived test systems have no requirements for trained laboratory workers.

She next described how tests are categorized and spoke of the three ways in which test systems qualify for CLIA waiver.

She presented the CLIA waiver history, stating that over a decade ago a rule that outlined CLIA waiver criteria was proposed by CDC and CMS. She went on to say that in 1997 the FDA Modernization Act clarified that all tests that are cleared for home use are automatically waived and that in 2005 a CLIA waiver guidance was drafted, which was published in January of 2008.

She identified the sources from which the guidance was derived and stressed the difference between guidance and the law, that the law is binding and guidance is not, that it merely recommends how to meet the law.

She then outlined the idea of using intended operators in a waived setting to perform testing of a proposed device while under the stress of multitasking, testing real samples over time, with two weeks being the minimum suggestion. She went on to say that the results of the waived test would be compared to another method, called a comparative method, on which the accuracy of the waived method could be based. She added that there would be traceability requirements for the comparative method, thus establishing a degree of trueness to the comparative method. She also said that the FDA would ask for a risk analysis on which to base flex studies and for clinically based performance standards on which to base accuracy, which have been identified as Allowable Total Error (ATE) and Limits of Erroneous Results (LER).

She continued by discussing the similarities and differences between

CLIA waived devices and Point-of-Care devices.

She asked how does a test system meet the CLIA waiver criteria and posited that the answer can be found in these two basic questions: Is the test system simple? Does the test system have an insignificant risk of an erroneous result? She highlighted points in the guidance as to what constitutes "simple" and described the recommended type of labeling and then explained that the question of insignificant risk can be addressed by the performance of risk analysis, the identification of all potential sources of error and the mitigation of these sources.

After elaborating on these points, she briefly discussed failsafe and failure alert mechanisms, giving examples of each, and then added that the flex studies that she had mentioned are stress studies that would be based upon the risk analysis. She touched upon potential sources of error, such as the use of expired reagents, reuse of cassette or reagent packs, and improper storage.

She recommended that clinical studies of devices proposed for waiver should be done in three clinical testing sites with at least nine different operators and that they should test 360 samples over a time period of a minimum of two weeks and, at the end of the study, be given a user questionnaire regarding the ease of use and the comprehensibility of the labeling.

She concluded her presentation by discussing the criteria for accuracy.

Marina Kondratovich, Ph.D., a statistician with the Division of Biostatistics, began her presentation by stating that she would be speaking about accuracy and some basic points related to accuracy, such as traceability, total error, Allowable Total Error zone, and Limits of Erroneous Results zone. She reiterated that the definition of the test for CLIA waiver is to employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible.

Discussing first the meaning of "accurate test," she presented the interpretation given in the FDA CLIA waiver guidance as those tests that are comparable to traceable methods or well-documented methods. She then went on to discuss the terms "comparable" and "traceable" and their meanings and noted, too, that the tests being discussed are quantitative, not qualitative.

She went on to discuss the basic idea of total error, comparing samples and methods used with two hypothetical patients. As in Ms. Benson's presentation, she also spoke of the FDA's recommendation that devices proposed for waiver be tested in three clinical testing sites with no less than nine operators on at least 360 different samples.

Speaking of the basic study design, she suggested that two different blood samples be obtained, i.e., finger stick and venous whole blood sample, and that the waiver method be performed by untrained users in the CLIA waiver setting, while the comparative method be performed by professional users in laboratory settings in order to evaluate the deviation of waiver

method results from the true value.

In order to ascertain what kind of deviation is acceptable, she explained the necessity of establishing Allowable Total Error zone, meaning that it contains very small errors or includes no errors and stated that it is anticipated that no less than 95 percent of sample results will fall within the Allowable Total Error zone. She then went on to discuss the Limits of Erroneous Results and emphasized the importance, from a clinical point of view, that the Allowable Total Error zone be as small as possible, and finding balance between the realistic expectation for test performance and the clinically acceptable expectation.

She next discussed how to set the Allowable Total Error zone, including the different rules when defining ATE for different ranges of comparative method and gave examples. She also discussed the kinds of approaches that can be used, such as published professional recommendations from national and international expert bodies.

She touched on the basic study design that Ms. Benson discussed in her presentation and gave examples.

She ended her presentation by asking the Panel for their input on Allowable Total Error zones and Limits of Erroneous Results zones for hematology devices.

PANEL QUESTIONS FOR SPEAKERS

During a brief question and answer session, Panel members questioned the first two speakers. Some of the topics covered were controlled cut-off studies, the source of 360 as the number for evaluation, flex studies, among others, followed by discussion among the Panel members.

FDA SPEAKERS

Robert L. Becker, Jr., M.D., Ph.D., Chief Medical Officer for the Office of In Vitro Diagnostic Device Evaluation and Safety in the Center for Devices and Radiological Health, spoke about laboratory and clinical issues attached to hemologic devices and especially to the potential use in a waived laboratory setting.

He began by outlining the four points of his presentation, which included a brief laboratory and clinical overview pertaining to peripheral blood counts, a description of hematology analtyes, practical challenges in counting blood cells, and a discussion on tradeoffs between depth of blood cell analyses and the cost of accessibility of testing, which should be considered in the context of a wide range of uses for blood cell counting that can help in framing the benefit and risks from waiver.

After stating that the FDA seeks the Panel's input concerning the suitability for waiver of devices used to obtain automated blood counts and differential cell counts, he then discussed the three kinds of results of CBC

studies and stated that indices such as mean cell volume and mean corpuscular hemoglobin would not be included in the discussion.

He went on to speak about differential cell counting and related that differential cell counts typically yield results for the five main classes of leukocytes and added that instruments providing either the fully specified or the less detailed versions of differential cell count would be a major focus for discussion.

He related to the Panel that regulations and FDA guidance provide key criteria for determining whether a device should be cleared for use in waived laboratories. Test simplicity, covered in Ms. Benson's presentation, was one requirement and another major requirement was that there shall be an insignificant risk of an erroneous result from the test as performed in waived laboratory settings.

He then gave a brief explanation of the two aspects of this second requirement: first, that the test should yield accurate results when performed accurately; and second, that the test should pose no unreasonable risk of harm to the patient if performed incorrectly.

In further discussion of this topic, he spoke of the morphological definition of basic blood cell classes, which dates back to Ehrlich's development of standing techniques in the late 1800s, and that ties between morphology and the roles for the various cell classes still persist today.

Manual or visual counting, implementation of guards against erroneous or misleading results, and microscopy-based visual methods were covered next. He also noted the FDA's recognition of Standard H20-A2, published by the Clinical Laboratory Standards Institute, for use in evaluating differential cell counters. He added that visual methods require much effort for precise counting of cell types that are present in low numbers.

After presenting a comparison of neutrophil counts against lymphocyte counts, he noted that the accuracy of some automated differential cell counters has been validated using visual counts of 500 or even 800 cells per specimen but that smaller numbers of cells are more normally visually counted, adding that for some new instruments, accuracy is checked solely against results obtained from another cleared, automated instrument.

He next described the two distinct groups that automated measurements fall into, hematocrit and hemoglobin, both being single-valued bulk measurements that are easy to automate and for which some devices are already waived by regulation. He related that the principal advantage of automated methods is the ability to characterize a large number of particles in a short time and that all automated methods rely on cell-by-cell measurement of physical or chemical properties that are correlates of cell morphology.

He spoke of common pre-analytical and analytical challenges which can complicate or degrade the performance of automated cell counters, which need diligence from personnel to recognize and avoid, and of challenges that are harder to recognize and are more subtle in their effects, such as antibodies which cause autoagglutination or rouleaux formation.

He next presented the differences between the signals that visual and automated counters use to do their work and gave examples of each. He noted that human readers integrate features such as size, shape, color and structure to classify cells, while automated instruments combine various electrical or optical signals to count and classify cells. Giving examples of three-part differential counts, he related that the most advanced instruments report all five main leukocyte types plus variant and pathological cell forms and then listed some of the conditions for which the blood count may be normal but examination of the peripheral smear will suggest a disorder to an informed observer.

Citing a study published by the College of American Pathologists, he reported that of the 263 hospitals and independent labs included in the study, more than one quarter of automated complete blood counts, including automated differentials, went on to some form of manual review and that among the laboratories in the lowest decile for blood film exams, nearly 10 percent of specimens had a peripheral smear examination. He also discussed an earlier Canadian study concerning automated testing of outpatients, which found that 35 percent of 1600 consecutive specimens were flagged, three-quarters of which had a corresponding abnormal finding in the blood film.

He advised that the key to successful testing is ensuring a match between the complexity of the test, the expertise of the testing personnel, and the expectations of the healthcare providers who use the results. He stated that the appropriate use of reference ranges is an important aspect of successfully applying the results of blood cell counts.

He stressed that CLIA certified laboratories must establish or verify reference ranges for the population tested and that consideration of the question of how the waived laboratories should evaluate and follow up results falling far outside an appropriate reference range is needed.

Presenting some of the potential significant benefits that waiver might bring for CBC and differential cell count testing, he related to the Panel that issues of adequate test accuracy and an informed review of test results will be part of the discussion framed by the FDA's questions to the Panel.

In conclusion, he listed the requirements for waiving in vitro diagnostic devices as simplicity, analytical accuracy, and insignificant risks and asked for the Panel's input on meeting these requirements.

Estelle Russek-Cohen, Ph.D., a team leader in the Division of Biostatistics of the Center for Devices and Radiological Health, stated that although her presentation also concerned statistical issues, she would be focusing on issues specific to CBCs and the automatic differential cell counting devices. She explained that she would first start by giving some background and terminology, and then go on to the topics of establishing accuracy, study conditions associated with the waiver study, allowable error, reference ranges and performance.

She began by contrasting the typical 510(k) versus the waiver and

related that in a 510(k) study, the sponsor often comes in and compares himself to an already marketed device for a similar intended use (which is called establishing substantial equivalence), whereas with waived devices, the sponsor is asked to compare himself to a comparative method to establish accuracy.

Not wanting to expand further on the topic of analytes that have already been waived by regulation, she focused, instead, on aspects of cell counting and spoke some more on the subject of imprecision and systematic bias, which had been discussed earlier, and then touched briefly on the topic of traceable methods.

Covering the topic of establishing accuracy, she acknowledged that although manual counts have historically been the referenced method, they are noisy and imprecise. She pointed out that sponsors have the option of averaging over multiple manual counts or showing that a well-established CBC device is traceable to manual counts and that they do this by citing literature or conducting their own in-house surveys. She then noted that if imprecision of the comparative method can be reduced, it is easier to pass. She went on to discuss a one-step design and an alternative two-part design.

She then presented a diagram illustrating the idea of traceability and then went on to discuss split sample design, such as two venous samples or a paired sample design (i.e., a finger stick blood sample and a venous blood sample), and that venous blood samples are done by professionals, while the waiver method is done by users at the waiver site.

Stating that the waiver study should mimic real clinical conditions and that the FDA would like to see the device use integrated into normal work, she reiterated that there should be, at the least, a minimum of two weeks but that two to four weeks is optimal. As discussed in the earlier presentations, she also suggested that the study should include three or more sites that are reflective of real-world use and that they should include nine or more users (who should not be laboratorians) with no more than three per site.

In discussing the study conditions and training, she specified that users should be aware of safe handling of blood specimens and that they should have access to the quick reference instructions, a package insert, and a 1-800 line, if offered.

She then suggested that quality control should also mimic real-world conditions and that, for the comparative methods, the results should be consistent with state and local requirements. She noted that typically there are no state and local requirements for waiver methods in a waived lab and added that quality control materials need to be recommended or provided by the sponsor. She also spoke of the need for sponsors to carefully consider the types of study sites that they choose so that they can find abnormal specimens as well as normal ones, since specimens need to span the measurement range.

Discussing the topic of Allowable Total Error, she spoke of the acceptable limits suggested by CLIA 88 and asked for the Panel's input regarding Limits of Erroneous Results, the definition, and patient results. She

then talked of clinical considerations with the Allowable Total Error and the Limits of Erroneous Results, that the indications and intended use populations for CBC and differential counts are very heterogeneous. Stating that the ATE and the LER should be specified to meet the most demanding intended use settings, she added that they might vary across the range of reportable values.

Discussing reference intervals, she questioned the Panel as to the likelihood of establishing a reference range in a waived setting. She then presented other options that the Panel may wish to consider.

In discussing performance, she explained that sponsors are asked to find low, medium, and high ranges for each analyte and that Allowable Total Errors and Limits of Erroneous Results be predefined. She pointed out that these are not just logistical considerations, but are serious clinical considerations.

Expanding further on performance criteria, she presented that one part is to capture bias because one of the concerns is the systematic differences between the waiver method and the comparative method. She suggested that this be done by study site, by low, medium, and high ranges, and that the sponsor consider using regression analyses appropriate to the data set. She stated that what is typically done is sponsors will provide scatter plots and regression lines and that they are asked to evaluate systematic bias at medically important concentrations and that the FDA is expecting negligible systematic bias.

The second part is that at least 95 percent of the waiver method value will fall within the Allowable Total Error region, that none of the values are expected to fall in the Limits of Erroneous Results, and that 95 percent two-sided upper confidence is bound to be less than 1 percent.

She concluded by asking the Panel to consider the following when answering the FDA's questions: what the Allowable Total Error should be for white blood cell differentials, what the Limits of Erroneous Results ought to be for all CBC analytes, and how reference intervals should be handled.

FDA SUMMARY

Ms. Bautista summarized the FDA presentation by making two points, the first being risk and benefit and the second being defining parameters to meet the waiver criteria, and finished her summary by asking the Panel for its input and assistance in helping to decide how to go about waiving these devices or even if they should be waived.

PANEL QUESTIONS FOR FDA SPEAKERS

During the next question and answer session, Panel members again questioned the FDA speakers. Some of the topics covered included analysis of outliers, waiving of hemoglobin single analyte instruments, the number of participants in the study and if there is any requirement on age ranges. At one

point **Dr. Sandhaus** pointed out that platelet count had not been mentioned and that she felt this needs to be addressed as well in the Panel's discussions. **Dr. Norback** asked that since there are no professional users with the waived instruments, would it be appropriate to insist that the machines themselves identify situations when they cannot give accurate results? Both **Dr. Kondratovich** and **Ms. Benson** answered in the affirmative. Other areas explored were outcome studies, untrained users, and comparisons between finger stick and venous blood samples.

GUEST SPEAKER

Judy Yost, M.A., MT(ASCP), the guest speaker, began her presentation by making the observation that when she first started in the laboratory field, only medical technologists performed the testing and that almost all of the testing was performed in a central laboratory on major pieces of equipment or manually.

She stated that CMS strongly supports Point-of-Care testing because of the access and convenience for patient care but still maintains the responsibility overall to ensure that all testing is accurate and reliable regardless of where it is performed and told the Panel that the focus of her presentation would be on the intent of CLIA, to ensure accurate and reliable testing.

She indicated that the percentage of entities performing testing with no oversight represented 60 percent of the 203,000 laboratories enrolled in the CLIA program and that CMS and its partners have all expressed concern about the testing performed by less educated and trained individuals with no oversight.

Presenting an extensive list of questions and concerns for the Panel's consideration, she indicated that she would only be addressing the key points in her discussion.

She next talked about background and data from the Certificate of Waiver Project and of the concerns that CMS has about the waiver of a CBC and differential. She stated that the only standard for Certificate of Wavier laboratories is to follow the manufacturer's instructions, that there is no PT required, there are no laboratory director qualifications, and the laboratory must enroll with CLIA at CMS. She reiterated that if a laboratory has a higher certificate, there is no oversight of waived tests.

Speaking of the findings of a study conducted by the states of Colorado and Ohio in 1999 in which it was discovered that 50 percent of the Certificate of Waiver laboratories visited had some sort of a quality issue, she reported that as a result of those findings, CMS expanded a pilot to eight additional states. It was found that 32 percent of the laboratories included in that pilot had quality problems. As a result, CMS went nationwide and is continuing to visit 2 percent of the Certificate of Waiver laboratories each year.

She explained that these visits are educational, that there is no statutory

or regulatory authority to actually survey these laboratories routinely. She told the Panel that CMS is allowed to visit, to collect information, to respond to complaints, and to provide education, and that is the basis for the ongoing project.

Moving on to statistics from 2006, she presented that approximately 37,000 or 31 percent of the laboratories visited were still not following the manufacturer's instructions.

Putting it into perspective, she related that in 1992, 30 percent of previously unregulated laboratories were not performing any quality control or following the manufacturer's instructions and that current data shows that the number is at about 5 percent because of routine oversight and the education that is provided to those laboratories. She pointed out that when laboratories that initially had problems are revisited, it has been found that up to 85 percent of them have demonstrated improvement because of the educational intervention.

She next discussed studies that CDC and the state of New York conducted in which their findings included the fact that high staff turnover occurred in waived testing sites and that there is lack of formal laboratory education, limited training of the individuals performing the testing, lack of awareness concerning basic good laboratory practice, how to collect and handle the specimen and how to accurately report results. The studies also found that partial compliance with manufacturers' quality control requirements was identified in 55 to 60 percent of those laboratories. She posed the question as to whether Certificate of Waiver laboratories and test device performance has improved sufficiently so that approval of a waived CBC test system will not be detrimental to patient care.

She reported that there are now about 100 analytes that are waived and that the number of laboratories that have a Certificate of Waiver has grown to 60 percent of the over 200,000 laboratories enrolled.

She next outlined CMS' concerns regarding the CBC waiver and posed these questions: Should an automated CBC and differential be categorized as waived? Does it meet the definition of simple and accurate? How does the device perform under real laboratory conditions? How are the varying hematological and patient populations addressed? What is the level of expertise necessary to operate the device and what level of judgment is necessary to interpret the test results? Is there any kind of data management capability for patient identification and to store and retrieve historical tests and QC results?

She then went on to address the issue of patient identification and some other concerns, such as maintenance, how extensive is it and what happens if it isn't done.

She also covered the issues of training, specimen collection, reagents, and quality control. In discussing reagents and quality control, she posed these questions: What are the test limitations? What are the types of precautions that the manufacturer has indicated in the package insert and will

these be flagged by the device? Is the package insert clearly written and concisely articulated? Is the test process time sensitive? What is the impact if the testing is delayed or the specimen sits? She also questioned the availability of manufacturers' quality control materials, if there are any at all, if the temperature they are stored at is the same as the reagents, and are they in the same box? She pointed out that the easier it is for a laboratory to use the quality control, the better chance there is of the laboratory performing that quality control.

She discussed patient testing under analytical and then moved on to post-analytical or the reports resulting phase of testing.

In summary, she asked the Panel these questions: Should an automated CBC and differential be categorized as waived? Does it necessarily meet the definition of simple and accurate? What is the level of expertise to operate the device and the judgment required in order to interpret the testing results? How does the device perform under real laboratory conditions using the actual testing personnel with no training? How are varying disease states and patient populations addressed in the result reporting and the analysis? Is there no risk of harm if these are performed incorrectly?

Concluding her presentation, she told the Panel that right now CMS believes that there are still significant enough potential areas of risk that must be addressed to reduce the likelihood of harm to the patient.

PANEL QUESTIONS FOR GUEST SPEAKER

During a brief question and answer session, the Panel questioned Ms. Yost on various issues, such as clarification of the meaning of following manufacturer's instructions; closing of laboratories, how often it happens and under what circumstances; why a substantial proportion of waived laboratories have no physician on site; why untrained and uneducated people should be allowed to draw blood samples; and if manufacturers can use Point-of-Care devices that have already made it through 510(k) as predicate devices for waiver application.

GENERAL PANEL DISCUSSION

The Panel then was then given the opportunity for discussion among themselves and for further questions of the speakers before moving on to the FDA questions.

Chairperson Adcock began by asking who drafts the flex studies and questioned whether there are requirements that these studies address areas of possible interference or potential complications. Further discussion covered topics such as the minimum number of samples required to do a flex study, failure testing, the high turnover in physicians' offices, among others.

FDA QUESTIONS AND PANEL DISCUSSION

Ms. Bautista read Question 1 to the Panel.

Question Number 1, Pre-analytical. In performance CBC/Diff tests, laboratory professionals traditionally control for a variety of pre-analytical variables such as hemolysis, gross presence of interfering substances, such as bilirubin and lipid, short or long sampling, or partial clotting, such as fibrin strands.

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

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

If the answer is no, please explain why.

The Panel members then gave their answers and opinions.

Chairperson Adcock's summary of Question 1 is that the Panel generally believes that CBC testing, as it is currently performed with known instrumentation, is not simple and there is the potential for clinically significant erroneous results. This may change should there be instrumentation developed that can properly identify the pre-analytical variables that the Panel is concerned about, and should an instrument be able to demonstrate such in an effective manner, then the Panel generally believes that waived testing may be applicable to such instrumentation.

Ms. Bautista moved on to Question 2. 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 in a submission for waiver categorization, please explain why.

The Panel members discussed Question 2 and **Chairperson Adcock** then summarized by saying that the Panel generally believes that there are many biological factors that may produce analytical variation that are pertinent to an instrument's proper analysis of a CBC sample, and that an instrument would have to have very secure failsafe 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 failsafes and identified enough of these analytical issues such that the testing would account for them. She noted that there are some serious questions as to how many samples would have to be evaluated and that there is concern that 360 would not be adequate to exemplify these potential analytical interferences.

She stated that the Panel also has some question as to what results would be reported and what comments would go on the report when there are either abnormal results or when there is a potential interference identified.

Ms. Bautista proceeded to the next question, 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?

The Panel members discussed their questions and comments, and **Chairperson Adcock** summarized that the Panel 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 wanted to note that omission of other results may be problematic because of the assumption that those results that are not reported may be incorrectly surmised by the clinician to be normal.

Ms. Bautista then read 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.

Following the Panel's discussion, **Chairperson Adcock** summarized by saying that there would have to be specific provisions established for follow up ofsome results because the instrument can generate critical or panic results. In addition to that, there would also be the potential for erroneous results to be generated and these would also require follow-up.

Ms. Bautista next read Question 5 to the Panel. How should the lack of trained operators in identifying post-analytical anomalous or incorrect result be addressed?

After discussion on this question, **Chairperson Adcock**, in summary,

said that given the current status of instrumentation, the panel generally believes that it would not be possible to have untrained personnel that could identify the post-analytical problems or incorrect results that may be generated, but if the instrumentation were to be advanced such that there would be fewer inherent errors, then it would be potentially possible to have such testing performed by untrained personnel or not formally trained personnel.

Ms. Bautista read 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 expressed 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.

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

The Panel members commented on and discussed Question 6a.

Chairperson Adcock's summary of 6a was that 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, specifically that the FDA consider the physiological variation and perhaps consider another method for evaluating the error, and it has been proposed that the locally smoothed median absolute difference curve analysis be considered.

Ms. Bautista proceeded on to Question 6b. For each analyte, what is the maximum error that would not endanger a patient's health?

There was Panel discussion, and **Chairperson Adcock** summarized that the Panel's opinion in regard to determining how the LERs should be obtained or determined for each of these analytes was that after significant discussion there was perhaps no real consensus. She stated that perhaps the LER should be redefined and replaced by clinically relevant zones and, for each of the zones measured, determine where clinical decision-making occurs., If results should vary in a significant manner, that is, to change clinical decision, this degree of variation would be different for each of the analytes and also along the different areas of each zone.

She also proposed that Dr. Becker's synopsis be taken to heart, that perhaps the LER should become a discrepant avoidance zone .

Ms. Bautista next read Question 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.

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.

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.

Following some discussion by the Panel, **Chairperson Adcock** summarized that the Panel generally feels that the accuracy standards as they are currently available would be the minimum and that the Panel would recommend more stringent numbers.

Ms. Bautista proceeded on to Question 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 suggested that the Panel defer this question, and **Chairperson Adcock** agreed.

Ms. Bautista then read the last question, Question 7, to the Panel.

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?

After discussion of Question 7 by the Panel, **Chairperson Adcock's** summary was that the Panel generally feels that QC is an 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 that would lockout the instrument in its entirety or a portion of the instrument.

ADJOURNMENT

Chairperson Adcock thanked the Panel, the FDA, the speakers, including the guest speaker and the public speakers, for their attendance and participation. She asked Dr. Gutman if he had anything to add.

Dr. Gutman thanked the Panel and his colleagues at FDA, CMS and CDC for their work on these issues.

Chairperson Adcock then adjourned the meeting at 4:49 p.m.

I certify that I attended this meeting on July 18, 2008 and that these minutes accurately reflect what transpired.

Louise E. Magruder
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

16 OCT 2008
Dorothy M. Adcock, M.D.
Chairperson

Summary Prepared by

Karen D. Martini
Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947
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