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SUMMARY MINUTES
OF THE
HEMATOLOGY AND PATHOLOGY DEVICES PANEL MEETING

SEPTEMBER 5, 1997

OPEN SESSION

9200 Corporate Blvd.
Rockville, Maryland

OPEN SESSION

Chairperson

Timothy J. O'Leary, M.D., Ph.D.

Executive Secretary

Veronica J. Calvin, M.A.

Voting Members

Diane D. Davey, M.D.

John L. Francis, Ph.D.

Yao-Shi Fu, M.D.

Nonvoting Members

Alton D. Floyd, Ph.D.
Industry Representative

Ellen S. Rosenthal, M.S.
Consumer Representative

Nonvoting Consultants

Brian S. Bull, M.D.

H. James Day, M.D., F.A.C.P.

John A. Koepke, M.D.

Simon O. Ogamdi, Ph.D., Dr. P.H., MT (ASCP), CLS (NCA)

Participating Members from Another Panel

Henry C. Nipper, Ph.D.
Clinical Chemistry and Toxicology Devices Panel

Robert Rej, Ph.D.
Clinical Chemistry and Toxicology Devices Panel

Guest Speaker

Barbara Gail Macik, M.D.
George Washington University

OPENING REMARKS

Executive Secretary Veronica J. Calvin, M.A., called the session to order at 10:45 a.m. She noted that the last panel meeting, held on September 27, 1996, concerned a premarket approval application supplement for a computerized automated Papanicolaou (Pap) smear reader indicated for use as a primary screener to select a subpopulation of smears to be designated for no further review. The panel voted eight to one in favor of disapproval of the application and recommended that clinical studies be done to investigate the safety and effectiveness in a laboratory setting. Ms. Calvin noted that this session was intended to discuss quality control issues for home-use prothrombin time (PT) devices and referred everyone to the specific questions to be addressed. Then she introduced Chair Timothy J. O'Leary, M.D., Ph.D, Division Director Steven Gutman, M.D., M.B.A., and asked all panel members to introduce themselves. Ms. Calvin read the conflict of interest statement and noted that various matters concerning Drs. Francis, Koepke, Day, and Bull had been considered. The matter concerning Dr. Bull was deemed not to pose a conflict, and waivers allowing full participation had been granted for the others. Guest speaker Barbara G. Macik had also declared financial interests that had been duly noted.

FDA PRESENTATION

Alfred W. Montgomery, D.V.M., acting branch chief of the

Clinical Chemistry, Toxicology, and Hematology Branch, began the FDA presentation by giving an overview of three recent regulatory developments. First, he noted an FDA pilot program to coordinate and use recognized standards in the 510(k) review process. Second, he mentioned a new paradigm being assessed to reclassify devices so that only Class II devices will be subject to premarket notification. Third, he discussed pilot testing of actual product development protocols or PDPs, based on early consultations between sponsors and the Food and Drug Administration (FDA) on device development, as an alternative to the premarket approval application process. He invited those interested in further information to attend an Office of Device Evaluation (ODE) workshop on the PDP.

Dr. Montgomery began the day's discussion by asking what kind of quality control (QC) is acceptable for home-use prothrombin time or PT devices in light of technological advances that are under way or on the frontier. He welcomed the contributions of additional consultants from other panels such as Drs. Nipper and Rej, as well as those from guest speaker Barbara Macik and FDA staff members Joe Jorgens and Valerie Dada. He asked panel members to consider the material presented on quality control testing of home-use devices and to provide their opinion to assist FDA staff in writing appropriate guidance. He noted that no vote was necessary but that it would be helpful to state areas of consensus.

Ginette Y. Michaud, M.D., medical officer in the Division of Clinical and Laboratory Devices (DCLD), reviewed the history of over-the-counter in vitro diagnostic tests since the passage of the Medical Device Amendments in May 1976. She noted that performance equivalence and performance verification are the two key analytical parameters considered by FDA in the review of these devices. She summarized the Agency's prior presentation to the panel on home-use PT tests and outlined the FDA's concerns for safety, quality control, adequate patient training, good analytical performance, patient follow-up, and the requirements for robust technology, physician supervision through prescription use, and good data collection. Dr. Michaud noted that the FDA cleared the first two home-use PT devices in 1997, using the panel recommendations as the basis of its regulatory approach, particularly in designating these devices for prescription use. She outlined both risks and benefits of home-use PT tests and asked the panel's advice on quality control (QC) issues relating to home-use technology. Dr. Michaud stressed the need for clear labeling recommendations regarding QC for home-use devices. The transition of a device into the home environment has led to a variety of quality control modalities, representing either a paring down of conventional QC or the introduction of novel approaches such as internal or built-in QC, electronic QC, or device self-testing process controls. The suitability of current QC approaches is presently being explored by groups such as the

National Committee for Clinical Laboratory Standards (NCCLS), the Centers for Disease Control, and the Health Care Financing Administration. Dr. Michaud concluded by stating that the FDA believes that the issue of QC in home-use devices deserves careful scrutiny to ensure that the method of verification is consistent with the robustness of the technology, variability in user skills and testing environments, and the risks posed by testing errors.

OPEN PUBLIC HEARING

Timothy O'Leary, M.D., Ph.D. opened the public hearing by noting that there were three scheduled presentations. The first speaker was **Michele Best**, MT (ASCP), testifying on behalf of the **American Society of Clinical Pathologists** (ASCP). Ms. Best addressed the need for careful evaluation of home-use prothrombin time devices, focusing particularly on problems involving the use of the International Normalized Ratio (INR) system used to standardize prothrombin time reporting across various reagent instrument systems, possible harmful effects of anticoagulation therapy dosages, and the risk of operator error in blood collection and result interpretation. She suggested an alternative solution of allowing use of these devices only in a local health care setting where the patient can be appropriately monitored and the device quality controlled. She concluded that very tight traditional QC, including two levels of standardized, traditional QC materials in the normal and therapeutic ranges,

should be mandated to supplement any electronic controls. In addition to QC and standardization of the device, rigorous patient education, training, and competency assessment must be included.

In response to panel questions, Ms. Best reiterated that two levels of traditional control should be used and that the controls and standardization must be built into the device as marketed. Devices could be used in conjunction with visiting home health care professionals and brought into a laboratory for checking every two to three months. She noted problems of checking for instrument drift and variations in specimen acquisition and stressed that two levels of external QC should be done each time the device is used, particularly while electronic controls are being assessed.

Rosemary C. Bakes-Martin, supervisory health scientist for the **Centers for Disease Control and Prevention** (CDC), spoke about two main areas of QC of concern to the CDC: the need for the QC system to address the potential for error and the need for measuring and monitoring quality over time. She noted three potential areas for error: the test system, the environment, and the operator, calling for robust and fail-safe devices with simple test designs, along with ample operator training. She noted that the operator was the area of most concern to the CDC, and she suggested that the health care professional should be part of the patient training and should supervise and assess

competency. On the need for monitoring over time, Ms. Bakes-Martin thought that two levels of testing every day were probably overkill and that enough fail-safe mechanisms in the device might make these traditional controls less appropriate, but she underlined the role of the health care professional in ensuring the device is working properly. The CDC does not recommend a specific frequency of device or competency testing; Ms. Bakes-Martin noted that it depends in part upon the device specifications.

In response to panel questioning, she elaborated that a minimum competency testing frequency should be mandated, but the specific recommendation was up to the health care professional, based upon device specifications and patient need. Several panelists raised concerns about patient training taking place in the setting of a physician's office; Dr. Koepke suggested using nurse clinicians to monitor anticoagulation therapy for periodic assessment. Ms. Bakes-Martin also suggested some external device testing reference, which did not necessarily have to be comparison to a laboratory device. She recommended periodic assessment of the device by health care providers at least whenever the patient is going to the physician for periodic checks, noting that the CDC had some difficulty with wet external controls being used in the home. It was suggested that organizations such as the College of American Pathologists might provide reference material for testing, particularly given that many home-use prothrombin time devices are whole blood devices

and the best controls available are plasma-based.

Alan K. Jacobson, M.D., FACC, spoke on his own behalf and on behalf of the **Anticoagulation Forum**, giving an introduction to testing issues for patients on anticoagulation therapy. He noted that as anticoagulation therapy becomes more widely used, the tolerance for problems in monitoring and the need for enhanced safety to optimize the risk-benefit of therapy become larger issues. He outlined the advantages and disadvantages of central laboratory testing, point-of-care professional testing, and point-of-care patient testing. He suggested that there was no medical basis for monthly testing, saying that the purpose of monitoring was to detect a change in steady state rather than a random variation and that greater testing frequency enabled better clinical decision-making capabilities. Dr. Jacobson noted as special considerations the fact that anticoagulation patients are above-average patients for reliability and that greater testing frequency leads to greater therapeutic benefit. He noted multiple levels of safeguards such as QC testing, internal electronic checks, periodic proficiency tests, and professional oversight of the results and asked the panel to ensure that QC mechanisms were good but based on clinical data.

In response to panel questions, he suggested once-a-week baseline screening and a recheck in two days for unanticipated results. He also noted that QC problems he has encountered have been with the QC agents rather than with patient error.

INDUSTRY PRESENTATION

Representatives of three manufacturers, Boehringer Mannheim Corporation, Avocet Medical, Inc., and International Technidyne Corporation, were scheduled to address the panel.

Richard Naples and Karen Roberts of Boehringer Mannheim Corporation (BMC) gave a manufacturer's perspective on quality control for home-use prothrombin tests. Mr. Naples gave a brief history of BMC's development of the CoaguChek system. Ms. Roberts outlined the manufacturer's responsibility in QC/quality assurance and contrasted features of laboratory versus self-testing, discussing these in detail. Ms. Roberts described the rationale for a home-use PT device QC scheme in terms of instrument, reagent, and operator and built-in checks. She outlined the elements of a quality management system as product development, patient selection, patient training, and maintenance of the patient's program. Mr. Naples concluded that the test developer is in the best position to determine appropriate QC recommendations, which should be based on technology, intended use/user, testing location, and overall quality management system of training and certification. BMC recommended that the FDA clear alternative QC strategies for home-use PT tests based on information that demonstrates equivalence between the traditional and alternative QC approaches. The FDA could also consider requiring postmarket surveillance on a product-by-product basis to demonstrate continued effectiveness of the QC frequency. BMC

also recommended that 510(k) submissions for alternative QC frequencies look at the instrument, the reagent, and the user in terms of the following: a failure mode and effects analysis, reagent stability data, external field studies, and an optional postmarket surveillance protocol.

Judith Blunt of Avocet Medical, Inc. spoke on special issues in home coagulation testing quality control, focusing on test accessibility and on preanalytic, analytic, and postanalytic variables. Preanalytic issues include sample collections, handling, and application. She discussed these issues in terms of prevention and detection of error through patient training and error checks. Analytic issues include reagent or strip integrity problems and meter function, and she described the Avocet Medical, Inc. PT device features that test for quality in these areas. On frequency of QC testing, Ms. Blunt said that appropriate liquid quality control testing would be two levels of QC testing with each lot of materials for the Avocet system, but that each manufacturer needs to validate that individually. She noted that when liquid QC controls are run, they should be at two levels and should challenge the medical decision levels, but liquid QC is inefficient, time-consuming, and expensive for routine QC. More efficient systems are available, and state-of-the-art diagnostic devices have on-board system checks that confirm functionality each time a device is used. Future QC protocols should consider these new developments in diagnostic

instrumentation. Manufacturers' data to demonstrate that component failures will be detected should be from the failure mode analysis and software validation required by the new FDA design control regulations. She concluded that the appropriate type and frequency of QC should be determined on a system-by-system basis for each device based on its features.

Carrie Mulherin of International Technidyne Corporation (ITC) discussed traditional quality control for laboratory tests, unitized test kits, and point-of-care (POC) systems. She noted quality control issues with patient self-testing, such as fingerstick technique and performing quality control. She described features of the ITC ProTime System that ensure accurate testing and QC compliance. She felt that the ProTime System does everything that traditional QC does in verifying the instrument, the reagent integrity, and user technique on each test through built-in electronic control. In conclusion, she gave an overview of the clinical trial and performance data for their device to demonstrate a quality system.

FDA PRESENTATIONS

Barbara Gail Macik, M.D., a guest speaker for FDA who is Associate Professor of Medicine at the George Washington University Medical Center, gave an overview of QC requirements, defining QC as a method employed to ensure that all test system components such as reagent stability, instrument function, operator consistency, and environment consistency are stable,

working correctly, and properly reported. She discussed NCCLS standards and the definition of usual and customary standards in a hospital or laboratory setting, asking whether these standards should apply to all settings. Dr. Macik described the differences between central clinical laboratories, small labs, and home use, with particular emphasis on how home testing differs from the laboratory. She discussed what information is necessary to establish QC requirements in terms of manufacturer data and in terms of home testing procedures and how many levels of QC material are appropriate for the normal and the therapeutic range levels. Dr. Macik defined electronic QC as a method to test instrument function through electronic monitoring of operating systems, either continuously internally or periodically externally through bar or magnetic codes. In discussing whether electronic QC is a reasonable alternative, she noted that electronic QC allows for a continuous monitoring of instrument function and is more likely to detect an instrument malfunction in a timely fashion, but will not test the entire system. After summarizing QC options such as liquid controls, internal electronic QC, and external electronic QC, she recommended that the FDA develop QC requirements specific for the test setting; that it rely on electronic control for primary monitoring of POC instruments; that manufacturers should provide data on validation of electronic control software, stability of reagent unit, and failure rate of instrument or reagent; and that wet controls be

used with every sample or not at all. In response to panel questioning, she suggested that an allowable error in QC would be plus or minus 0.5.

Joseph Jorgens, III, J.D., a biomedical engineer from the **Medical Imaging and Computer Applications Branch**, described software engineering concepts in considering the approach the FDA takes toward hardware and software. He noted that QC is a mature industry from a hardware point of view, but there is not a similar quantification of risk for software. Observing that one cannot "test in" quality for a software product, he said that manufacturers must implement software engineering procedures as the software is designed. He listed five concepts to be included in software review guidance: hazard analysis to determine possible hazards to the patient; functional requirements and systems specifications; software design and development; verification, validation, and testing of the software product; and revision control procedures.

Valerie Dada, MT (ASCP), a hematology scientific reviewer in the Clinical Chemistry, Toxicology, and Hematology Branch, thanked the panel for its assistance, noting that the FDA was sensitive to the issues and concerns raised by the various interest groups and industry representatives. She reiterated the importance of QC testing in guaranteeing the assurance of patient safety. In conclusion she reminded the panel that in the professional domain the QC testing standard for non-manual

coagulation devices remains two levels of QC material which should be tested every eight hours, repeated each time the reagent changes, and she presented seven FDA questions for panel discussion.

OPEN COMMITTEE DISCUSSION

Panel members had a range of views on the frequency of appropriate QC testing, although in general several panelists agreed that the frequency depends on the specific device. Dr. Rej recommended that the frequency should be linked to clinical data, and that a QC component should be built in to check the reagent. Dr. Ogamdi suggested at least one external control each day the test is used. Dr. Koepke suggested one rather than two at the therapeutic level. Dr. Davey, Dr. Day, and Ms. Rosenthal suggested running QC each time the test is run, saying that the QC does not have to be external but companies need to provide much data from postmarket studies if nontraditional methods are used. Dr. Davey said that a test of reagent stability and a lockout capability if there is a system error are both essential.

Dr. Nipper recommended two concepts: an allowable error, estimated by FDA studies, above which the potential for harm is high; and an appropriate action range. He agreed that the number of QC levels, action limits, and frequency can be tailored to the device, saying that QC could not be established as daily or weekly but had yet to be determined for each device. Dr. Floyd saw the gray area as the testing of reagent stability. Dr. Francis agreed that it is essential to have QC every time the

test is run, at least of internal QC, although not necessarily external QC. He suggested postmarket survey data on what is the acceptable error rate. Dr. Bull suggested the need for a study on the operating curve on turnaround time versus variability in home testing. He saw the biggest problem as patient training and felt that manufacturers should check on such training. He suggested package controls and occasional random checks.

On the second question, concerning how many levels are appropriate, most panel members agreed that two levels are not necessarily the right answer, although some argued for two levels until more data are amassed.

On the role of routine QC in detection of device failures, panel members suggested a lockout capability, particularly to evaluate patient incompetency at testing. Several members agreed on the importance of good electronic controls built into the device and on the importance of hazard verification. Panelists also agreed on the need for more data on machine use over long periods of time; Dr. O'Leary and Dr. Day noted the need for accelerated aging procedures and drop testing.

On the incorporation of software for statistical analysis of QC results, panel members agreed that such software analysis would be useful, but the ranges of deviation should be based on clinical data. Several agreed that the machine should calculate the results and provide a lockout feature based on internal QC data stored in the software. The machine could also signal an alert if the data trend is in the wrong medical direction. Dr.

Bull suggested that the machine memory could store patient results, with the patient being told to repeat the test if there is a significant change. Such results could be stored for two to three months or even for years using statistical filters to detect instrument drift. Panel members agreed that postmarket surveys are important to determine failure modes.

Issues warranting special consideration in choosing appropriate QC included sample verification and preanalytic variation, postmarket surveys, fail-safe and lockout mechanisms to ensure that patients obtaining unanticipated results will see their physicians, possibly with the lockout feature tied to the physician's phone number, and training adequacy and competency certification or licensing. Use of video materials for training and retraining was also recommended.

Dr. Nipper suggested that lot-to-lot variability in QC values should be considered to ascertain that wet QC does not give false rejections.

Panel members suggested paying equal attention to consumable or reagent parts of the test system and to developing a good control system for travel and at-home tests. They called for a more idiot-proof home as well as laboratory system and for more postmarket survey data, particularly on the use of liquid controls.

Dr. Steven Gutman thanked the panel members and invited all those present to submit further ideas on the Internet or through upcoming Open Forums. Veronica Calvin thanked the former

executive secretary of the panel, the chair, the public and guest speakers, and the FDA staff members, as well as the panel, for their help. Dr. O'Leary thanked the FDA staff and the panel and adjourned the meeting at 4:30 p.m.

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I certify that I attended the Hematology Devices Panel Meeting on September 5, 1997, and that this transcript accurately reflects what transpired.

Veronica J. Calvin

Veronica J. Calvin, M.A.
Executive Secretary

I approve the minutes of this meeting as recorded.

Timothy J. O'Leary

Timothy J. O'Leary, M.D., Ph.D.
Chair

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