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MEETING OF THE RADIOLOGICAL DEVICES PANEL

May 17, 1999

OPEN SESSION

**Corporate Building
9200 Corporate Blvd.
Rockville, Maryland**

**Participants in the Radiological Devices Panel Meeting
May 17, 1999**

Voting Members

Brian S. Garra, M.D.
Chair

Judy M. Destouet, M.D.

Arnold W. Malcolm, M.D.

A. Patricia Romilly-Harper, M.D.

Nonvoting Member

Marilyn R. Peters, M.N., M.P.H.
Consumer Representative

Temporary Nonvoting Members

Harry K. Genant, M.D.

Kenneth G. Faulkner, Ph.D.

Joan McGowan, Ph.D.

Charles H. Turner, Ph.D.

Raymond P. Silkaitis, Ph.D.
Industry Representative

Guest Speakers

Dennis M. Black, Ph.D.

Anne C. Looker, Ph.D., R.D.

Paul D. Miller, M.D.

Alan M. Tenenhouse, M.D., Ph.D.

Richard D. Wasnich, M.D.

Industry Speakers

Christian M. Langton, Ph.D.

Richard B. Mazess, Ph.D.

Daniel Michaeli, M.S.

Eric von Stetten, Ph.D.

FDA Participants

Robert J. Doyle
Panel Executive Secretary

Larry Kessler, Sc.D.
Director, Office of Surveillance and Biometrics

Daniel Schultz, M.D.
Director, Division of Reproductive, Abdominal, and Radiological Devices

Thomas Shope, Ph.D.
Office of Science and Technology, CDRH

William Sacks, Ph.D., M.D.
Office of Device Evaluation, CDRH

OPEN SESSION-MAY 17, 1999

Panel Chair Dr. Brian S. Garra opened the meeting at 9:02 a.m., noting that the voting members present constituted a quorum and asking all members to introduce themselves. Executive Secretary Robert J. Doyle stated that panel member Alicia Y. Toledano would not be able to participate in the session because of a personal medical emergency. He read the conflict of interest statement and noted that Drs. Genant and Faulkner had been granted full waivers allowing their participation despite interests in firms potentially affected by matters under discussion. Matters unrelated to the panel discussion involving Drs. Turner, Garra, and Romilly-Harper had been considered, and their full participation allowed. Drs. Miller, Tenenhouse, and Black had declared interests involving firms at issue but would be allowed to participate as guest speakers.

Mr. Doyle announced two tentative future panel meetings on August 16 and November 18, 1999. He noted that two premarket approval applications had been approved since the last meeting: for the R2, M1000 mammogram image analysis system in June 1998 and for the TransScan T-Scan 2000 multi-frequency impedance breast scanner in April 1999.

Dr. Thomas Shope of the FDA's Division of Electronics and Computer Science gave the panel an update on the Y2K date problem in computerized medical devices. He listed the types of medical devices that are subject to Y2K problems and defined the Y2K problem. He also read a definition of Y2K compliance. Dr. Shope asked the panel to provide advice regarding problematic devices, identify types of devices that could present risks to patients because of date problems, and suggest actions to reduce risks from Y2K problems. Advice should be sent to him in the Office of Science and Technology or to the Panel Executive Secretary Robert J. Doyle.

Dr. Shope summarized FDA/CDRH activities on the Y2K problem to date. He noted that the FDA has a biomedical equipment database on its World Wide Web site that is continually updated and contains voluntary submission of data provided by manufacturers. He gave the FDA web page address for the FDA product database (www.fda.gov), noting that information is posted there on Y2K compliance as it is received from manufacturers. The database shows that many companies have not yet reported. Most of the noncompliant products have date stamping problems, but a limited number have operational problems. Manufacturers are providing a variety of solutions. The FDA can require recall of devices presenting a significant risk to public health and will monitor reports of Y2K problems with emphasis on devices that could present significant patient risks. Dr. Shope also listed future CDRH/FDA activities and healthcare facility issues.

Dr. Larry Kessler Director of the FDA's Office of Surveillance and Biometrics gave the panel a presentation on postmarket surveillance and methods of postmarket evaluation at CDRH, focusing on the pivotal role of the advisory panel in postmarket evaluation. He listed six methods of postmarket evaluation and the issues to be considered during the postmarket period. Dr. Kessler also described the Medical Device Reporting (MDR) Program, which provides limited but critical information to FDA about devices with problems, and he listed the possible actions prompted by such a medical device report along with examples. Dr. Kessler discussed the two postmarket authorities, postmarketing surveillance and postapproval authority, and outlined the criteria for a panel to suggest postmarketing surveillance as well as study designs used in such surveillance. He challenged the advisory panel to ensure that a postmarketing study will be of primary importance, to specify the public health question it is to address, and to note what will

be done with the data collected. In conclusion, he briefly outlined the future for the MDR and Postmarketing Surveillance programs.

OPEN PUBLIC HEARING

Three individuals had asked to address the panel.

Dr. Louis H. Sherwood, of Merck & Company and the Bone Measurement Institute, discussed the evolution of bone mineral density (BMD) in clinical practice. He reviewed the mission of the Bone Measurement Institute since its 1995 founding and described the situation in 1999. He concluded that the T-score, while not ideal, is used widely to serve many valuable purposes. T-score issues can be addressed by adjusting for device and database differences and linking T-score to fracture risk, and he suggested that cholesterol as a predictor of cardiovascular risk is a good model. He concluded by defining BMD measurement as a public health issue and underscored the need to have BMD understood by primary care providers and patients.

Dr. Ethel Siris of the National Osteoporosis Risk Assessment (NORA) discussed the clinical utility of T-scores as observed in a study of peripheral BMD and fracture risk. She described a study of 204,000 postmenopausal women and a current substudy of 76,000 women and presented findings in terms of fracture incidence as correlated to age, ethnicity, and T-score.

Dr. C. Conrad Johnston of the National Osteoporosis Foundation (NOF) observed that recent studies indicate the usefulness of bone density studies in predicting future fracture risk. He suggested that the challenge is to determine the clinical utility of the new techniques entering the market place. NOF has established a committee to study this matter and to solve the issue of cross calibration between technologies. The issue of using gender-specific and race-

specific data bases in assessing fracture risk is likely to call for further study, particularly on what cut-points should be used for intervention.

OPEN COMMITTEE DISCUSSION

Charge to the Panel

Dr. Garra noted that the purpose of the meeting was to discuss bone strength assessment, with a focus on the use of gender- and race-specific databases in assessing fracture risk, and their applicability to bone densitometry and sonometry device labeling.

Introduction

Dr. Daniel Schultz noted that new diagnostic and therapeutic products in the field of bone strength assessment have led to more questions as well as answers and produced uncertainty about how to proceed. He emphasized that the FDA's role is not to dictate the practice of medicine but to provide a reasonable assurance of device safety and effectiveness.

Key Issues for Panel Consideration

Dr. William Sacks outlined key issues for panel consideration. He sought panel advice on labeling and output of bone diagnostic devices. The three primary current forms of measurement are the absolute values of bone mineral density or quantitative ultrasound versus the T-score, which is related to young normal women, and the Z-score, which is an age-matched comparison. He asked the panel to compare their clinical utility for age-related bone loss and for other medical conditions. Another issue is the use of a common white female database versus various gender and ethnic databases and the need to define specific issues for the gender and ethnic databases.

Dr. Paul Miller of the Colorado Center for Bone Research discussed the history and basis for the WHO paradigm. He cited the 1991 Consensus Development Conference definition and the 1994 WHO BMD definition of osteoporosis. He described the calculation methods used to determine the T-score. After looking at data from the National Health and Nutrition Examination Survey (NHANES) normative database, he concluded that T-score discrepancies exist due to reference population differences, skeletal discordance in individuals, and technology differences. He also described the WHO criteria, which are based on prevalence and approximation of lifetime fracture risk in a cross-sectional population-based study of postmenopausal Caucasian women with an arbitrary cut-off point of <2.5 SD. However, since the relationship between risk of fracture and BMD is a continuous gradient, no criteria are capable of distinguishing an individual who will fracture from one who will not. He then listed the strengths and limitations of the WHO criteria for the diagnosis of osteoporosis.

Dr. Richard Wasnich of the Hawaii Osteoporosis Center discussed whether there is a basis for race and gender measurement differentiation. After defining the issue and its significance, he considered the primary and secondary evidence relating to race and gender. He concluded that in 12 prospective studies in 14 locations on various ethnicities and races and in both men and women, the independent relationship of bone density to fracture is remarkably consistent, irrespective of fracture type or bone measurement site and/or technology. He noted that T-scores and Z-scores are derived solely from age-related population values and are not based upon fracture risk. Absolute fracture rates can be used directly for clinical decision-making. Other risk factors such as age or prevalent fracture can easily be incorporated into the absolute fracture risk estimate. Dr. Wasnich concluded that it is time to improve the clinical

paradigm by converting bone measurement to absolute, global fracture risk. The continued use of arbitrary cutoffs and T-scores results in the wrong patients being treated. He said that the only potential utility of normal young reference databases is for evaluation of patients under 30 as a measure of skeletal development; young normal databases are useless and misleading for purposes of fracture risk estimation in older patients. Since neither gender nor race affects the relationship between bone density and absolute fracture risk, there is no need for arbitrary scales. Physicians should be told that treatment decision should not be based upon bone density levels alone, but should be based upon all risk factors and expressed as absolute fracture risk. Physicians also need to be reminded that low bone density is a manifestation of multiple diseases and conditions.

Dr. Charles Turner, of the Orthopaedic Surgery Department at Indiana University discussed the physical bases for the noninvasive assessment of bone strength from an engineering perspective. He asked how measurements predict bone fragility, which predicts fracture risk. He noted that fracture risk is determined by lifestyle issues that contribute to trauma and skeletal fragility. While many factors contribute to bone fragility, BMD gives the best radiological assessment of fracture risk. Ultrasound velocity and BUA correlate with bone strength as well or better than BMD. These measurements provide structural information about the bone beyond that provided by BMD.

Dr. Harry Genant of the Department of Radiology at UCSF gave a comparison of common BMD techniques in patient classification using data from 5,568 women from the Study of Osteoporotic Fractures (SOF). The SOF study found the correlation between BMD measures to be good, but the agreement in threshold-based classification to be only modest. **Threshold-**

based classifications depend heavily on the reference data used, and standardization of the reference data will reduce but not eliminate the inconsistency between classifications. Given low BMD at one site, low BMD at another site may further increase the risk of hip and/or spine fractures. Classification of an individual patient based on one borderline normal/abnormal BMD measurement using a specific threshold may be unreliable, and employing an additional BMD measure in this setting may have clinical relevance.

Dr. Anne Looker of the National Center for Health Statistics discussed the effects of race- and sex-specific cutoffs on prevalence estimates from the National Health and Nutrition Examination Surveys (NHANES III). After a brief outline of the sample design used in the survey of 14,600 people, she concluded that the use of race and sex-specific cutoffs results in higher cutoff values for men and black or Mexican American women than for white women. The pattern of prevalences is less consistent with fracture pattern by race or sex. Using white women cutoffs is the most conservative approach because these are the lowest cutoffs.

Dr. Alan Tenenhouse of McGill University described the primary objectives, study design, demographics, and results from the Canadian MultiCentre Osteoporosis Study (CaMos) of 7,500 males and females. Study results were very similar to those found by NHANES for non-Hispanic Caucasians in the United States but were very different from those used as DEXA references by the manufacturers. The only factors found to affect PBM were BMI, height, and center. After adjusting for BMI and height, center remained a strong determiner of PBM. It is not yet known whether this translates into a different prevalence of low BMD in later life and/or increased fracture risk. Preliminary analysis of vertebral deformity prevalence shows no difference between women from these centers.

Dr. Dennis Black of the University of California, San Francisco, gave a comparison of T-scores, Z-scores, and other measurements for assessing fracture risk. He discussed the use of T-scores versus Z-scores and whether T-scores were comparable across devices. He concluded that application of T-score cut-points across sites and devices does not yield comparable prevalence of low BMD and fracture risk across sites. Thus, T-score cut-points cannot be applied uniformly to all sites, devices, and technologies. Much of the T-score discrepancy is due to differential bone loss at different sites, and the risk discrepancies are also due to stronger relationship of BMD to fracture at some sites. Because the generalizability of T-score-based cut-points to other ethnicities and genders is unclear, T-scores may not be the best way to standardize across gender and racial groups.

Dr. Black described a proposal to alter use of BMD to diagnose osteoporosis by using an absolute risk format with a cutoff of a certain value. He suggested creating device-specific diagnostic cut-points to anchor T-scores, which he called “T-score equivalent cut-points.” He presented the data and models required for these cut-points and the preliminary assumptions behind the current proposal. Use of device-specific cut-points would provide a unified framework for rational incorporation of new devices.

Industry Presentations

Dr. Christian Langton for McCue PLC discussed whether fracture risk is better predicted by physical properties than by T-score. He discussed the science of quantitative ultrasound (QUS) and the clinical potential for its use in predicting fracture risk and referring cases for subsequent conventional densitometry. He also discussed whether the WHO criteria can be applied to QUS and compared device-specific parameters versus use of the T-score. He

proposed that any future strategy should define both its purpose and a gold standard for assessment. Health economics should also be a factor.

Dr. Richard Mazess of Lunar Corporation analyzed sources of variation in T-scores. He listed five factors causing T-score differences, such as differences in rates of bone loss at different skeletal sites or differences in standard deviations around the mean. He suggested two solutions to T-score differences: limiting WHO categories to variables with normal aging loss and developing equivalent T-scores based on prevalence and/or risk.

Dr. Eric von Stetten of Hologic, Inc. reported on bone densitometry results. He discussed a PMA supplement his company had submitted at the end of 1998 that contained databases of Caucasian males and African American females for use with densitometry devices. He listed the advantages and, limitations of ethnicity and gender matched databases. Questions from panel members focused on their concern about quantifying fracture risk with a direct correlation of this information.

Daniel Michaeli, M.S. of Schick Technologies, Inc., gave a presentation on giving clinicians useful and simple guidelines without creating confusion. He discussed the state of bone densitometry in 1999 and the limitations on usefulness of T-scores. He mentioned physician confusion over use of the T-score or a T-score equivalent and when such information warranted treatment, confusion shared by medical care payers as well. He concluded with the hope that in the future clinicians would advise individuals with the best information available regardless of age, ethnicity, gender, or densitometer and that payers, clinicians, and patients would realize the importance of bone densitometry in assessing osteoporotic fracture risk.

OPEN PUBLIC HEARING

Cindy Pearson of the National Women's Health Network recommended that the panel advise the FDA that the fracture and osteoporosis risk for women of color is an important research question. She also discussed the risks of over-treatment for false positives and asked the FDA to balance information on the need for testing to prevent the real suffering caused by osteoporosis against the incorrect assumption that one positive test result warrants drug intervention. She recommended labeling information about the test for the patient. There were no other requests to address the panel.

OPEN COMMITTEE DISCUSSION

Executive Secretary Robert Doyle presented the FDA discussion points. **Dr. Kenneth Faulkner of the Oregon Osteoporosis Center** was the lead discussant.

In discussing the roles of absolute values, T-scores, and Z-scores, the sense of the panel was that there is a need for absolute values. Until more information is gathered, however, the T-score should remain a useful tool in assessment of fracture risk and patient management, particularly if tied to other risk analysis techniques. The present is a transitional period for fracture analysis, and BMD may eventually replace T-values. Absolute fracture risk data presented in a standardized way in controlled case studies would go far in helping the transition from T-scores. Z-scores are important for other indications and assessing secondary conditions, although there was some disagreement on this point. The panel was interested in the concept of T-score equivalents but would wait to see how the NOF, ISCDN, and other studies progressed.

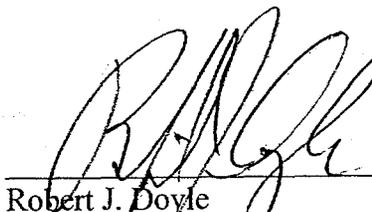
On the need for appropriate databases and their use, the sense of the panel was that comparisons to a single standardized young, white, female database in assigning appropriate

levels of fracture risk to individuals have utility. Gender and ethnic databases also have some utility, although these are not appropriate for fracture risk analysis. There was panel concern about misuse of the database for fracture risk assessment with no prospective data. To clarify the relationship between BMD and fracture risk, the panel urged cross-sectional cohort studies to provide acceptable standards. The need for standardization requirements for valid measurements and for quality assurance was also stressed. The use of standard curves and phantoms should be developed for use with DEXA.

On labeling concerns, the panel urged that indications for use should include training and certification on the use of all bone assessment devices, as well as performance standards. A consistent set of standards, sites, and equipment was urged. Guidelines for careful case control studies should be developed. A precaution or warning was suggested that the use of the ethnic databases had not been clearly defined and their use for the risk of fracture risk assessment had not been established.

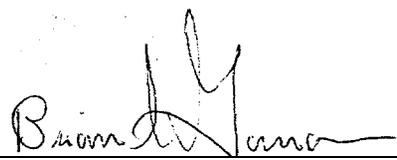
Panel Chair Dr. Garra thanked the panel and all participants in the meeting, as did Dr. Schultz on behalf of the FDA. The meeting was adjourned at 5:10 p.m.

I certify that I attended the Open Session of the Radiological Devices Panel Meeting on May 17,1999, and that this summary accurately reflects what transpired.



Robert J. Doyle
Executive Secretary

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



Dr. Brian S. Garra
Chair

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