Bone Sonometer PMA Applications; Final Guidance for Industry and FDA

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Center for Devices and Radiological Health

Radiological Devices Branch
Division of Reproductive, Abdominal, and Radiological Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Robert Phillips, Ph.D. at (301) 594-1212 extension 160 or by email rap@cdrh.fda.gov.

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This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

I. INTRODUCTION

This guidance identifies for the manufacturer special issues associated with bone sonometers that the Food and Drug Administration (FDA) has determined will assist in providing assurance of reasonable safety and effectiveness.

The PMA application should be on standard 8.5" x 11" paper and include the original with twelve (12) copies. Provide a volume containing all the electromagnetic compatibility (EMC) information and another volume containing all the software data. The manufacturing software information contained in the manufacturing section should be duplicated and included in software volume.

This document describes the information that is unique to a sonometer PMA application. For the general information that also should be included in a PMA application, refer to the following documents:

Premarket Approval (PMA) Manual (http://www.fda.gov/cdrh/manual/pmamanul.pdf)

Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers (http://www.fda.gov/cdrh/ode/ulstran.pdf)

Medical Device Labeling--Suggested Format and Content (http://www.fda.gov/cdrh/ode/labeling.pdf)

Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers (http://www.fda.gov/cdrh/ohip/guidance/1128.html)

Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (http://www.fda.gov/cdrh/ode/software.pdf)

Labeling Reusable Medical Devices For Reprocessing In Health Care Facilities: FDA Reviewer Guidance (http://www.fda.gov/cdrh/ode/198.pdf)

Designing, testing, and labeling reusable medical devices for reprocessing in health care facilities: A guide for device manufacturers, 1st Ed., AAMI TIR 12:1994

Alternative to Certain Prescription Device Labeling Requirements (http://www.fda.gov/cdrh/comp/rxlabeling.html)

We recommend that you contact the agency prior to initiating any clinical studies.

II. THE LEAST BURDENSOME APPROACH

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

III. GENERAL INFORMATION

See "Premarket Approval (PMA) Manual"

IV. SPECIFIC INFORMATION

A. Indications for Use

The indications for use may have one or more of the following components:

1) determining the possible presence of osteoporosis and assessing fracture risk,
2) monitoring bone changes over time, and
3) assessing non-age-related bone loss.

The PMA application should clearly state those indications for which approval is being sought. An example is "The [device] performs a quantitative ultrasound measurement of bone, the results of which can be used in conjunction with other clinical risk factors as an aid to the physician in the diagnosis of osteoporosis and medical conditions leading to reduced bone density, and ultimately in the assessment of fracture risk."

B. Device Description

1. Sonometer

You should provide the complete explanation and description of the device. In addition to the items requested in the Premarket Approval (PMA) Manual, the following items should be provided:

a) physical description

b) engineering or block diagrams showing the major components

c) the purpose of each component

d) copies of all pages that are displayed either on a CRT screen or in a printed copy

e) detector technology

f) a block diagram of the operating program

g) the number of bits in the A/D converter and the digitization rate

h) calibration standards used (built-in and external)

i) anatomical site(s) scanned and a discussion of how you chose the target area within the anatomical site(s) and your rationale

j) a description of the algorithms for computing the measurements, e.g., broadband ultrasonic attenuation (BUA) or speed of sound (SOS), in detail

[Note: Any underlying assumptions should be delineated. For example, you should specify the particular marker on the pulse waveform for measuring transit times for SOS computation (e.g. first zero crossing, envelope maximum, first zero crossing prior to the envelope maximum, etc.). For BUA, specify the bandwidth used in the calculation of attenuation versus frequency. The algorithm (e.g. difference of the logarithms of the spectra of attenuated and reference signals) should be described. The purposes and implementations of any filters applied to the received data should be described.]

k) a description of the algorithms used to analyze the data and to calculate the values presented (T- and Z-scores, etc.)

l) the transducer specifications including diameter, resonant frequency, bandwidth, focusing properties

m) beam description (e.g., size, spectra, intensity), including the average and maximum acoustic intensities measured for the device (e.g., $I_{SPPA.3}$, $I_{SPTA.3}$, MI - See "Information for Manufactures Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers.")
Fully describe your measurement methodology.

2. Phantoms

If the device employs phantoms, i.e., quality control, maintenance, etc., in procedures, please provide the following additional information:

a) State which devices are compatible with the phantom and which phantom(s) are to be used for the device.

b) Explain how the phantom(s) are used.

c) Discuss the construction, including contents of a phantom(s).

d) Provide a copy of the user manual(s) for the phantom(s), which should include the indications for use of the phantom(s).

e) Provide a product sheet detailing the technical and descriptive specifications of the phantom(s).

3. Accessories

List the options and accessories. Provide technical information on all options or accessories that you are including in this PMA application.

C. Laboratory Testing

1. Describe the developmental steps and testing taken to ensure good coupling between the ultrasound and the skin surface (e.g. use of coupling gel for dry systems). In the case of wet systems, the methods for eliminating bubbles and for preparing the skin (e.g. cleaning with alcohol pads) should be specified. This information should also be provided in your labeling.

2. Provide the results of testing that you performed to establish the precision and accuracy of measured values (e.g., BUA, SOS).

3. Describe the procedures and testing that you performed to validate your recommended user quality assurance schedule and tests. Describe any phantoms that you either provide or recommend for this purpose. Many commercial ultrasound phantoms have acoustic properties that drift over time. An analysis of the long-term stability of acoustic properties of test objects should be provided.

4. Describe the verification and validation procedures performed to support your recommendations for cleaning and disinfecting the system between patients.

D. Clinical studies

Clinical investigations are necessary to establish reference database(s), the precision and accuracy of measurements, and fracture risk estimation.

1. Recommended exclusion criteria for bone sonometer study subjects.

a) Current or recent use of bone-active drugs
   Bisphosphonates, more than 1 week *ever*
   Calcitonin, within 3 months
   Therapeutic doses (>1000 I.U. daily) of vitamin D, within 6 months
   Estrogens or SERM within 6 months
   Therapeutic doses (> 2 mg/day) fluoride within 3 years
   Drugs under research protocols within 2 years
   As yet unstudied or unapproved drugs – investigator's discretion

b) Presence of metabolic bone disease
   Hyper- or hypo-parathyroidism within 5 years
   Osteitis deformans (Paget's disease of bone)
   Renal osteodystrophy
   Osteomalacia

c) Gastrointestinal malabsorption

d) Liver disorders

e) Chronic renal disease

f) Unstabilized hyper- or hypothyroidism

g) Hyper- or hypoadrenocorticism

h) Concomitant use of oral corticosteroids, if less than equivalent of 7.5 mg daily of prednisone, within the past 6 months; if greater dosage, then within the past year.

i) Use within past 6 months of anti-seizure drugs, barbiturates, or anticoagulants

j) Stroke with total or partial paralysis with residual disability lasting more than 3 months

2. Reference Databases

a) T-Score

T-score, as used by WHO (*Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis*, World Health Organization, WHO Technical Report Series 843, 1994) in their definition of osteoporosis, is the patient's reading minus the average reading of healthy young (between 20 and 39) Caucasian females divided by this group's standard deviation. Reference databases of non-Caucasian females or males of any ethnicity are not appropriate for T-score calculation, unless new action levels are also developed.

You should develop a normative reference database of at least 300 healthy, Caucasian women between the ages of 20 and 39 with at least 150 subjects in each decade. (Note: The sample size of 300 subjects is at the lower end of the optimal range of 300 to 500 subjects according to Martin et al., Normal Values in Clinical Chemistry, Marcel Dekker, 1975, pages 51-52.). At least two geographically separated sites should be used.

b) Z-Score

The Z-Score provides a comparison between an individual patient and the average of a population of the same age, gender, and ethnicity. Databases for different ethnicity and genders are appropriate. Use of Z-scores plays a role only in the detection of causes of abnormal bone other than age-related bone loss but has no role in fracture risk assessment. Gender- and ethnic-specific normative databases, across all ages within the range of interest (generally from 20 to 80 or 90), should be provided with sonometry devices to facilitate interpretation of bone measurements for evaluating secondary (non-age related) causes of low bone mass and osteoporosis.

Databases for each ethnicity and gender should consist of measurement results from at least 50 subjects per institution per decade for the range of decades of interest. At least two geographically separated sites should be used. These databases should be analyzed by decade and the mean and standard deviation of the appropriate bone sonometer measurement for each decade presented. Statistical models should be developed to model the ultrasound bone measurement vs. age. These models may be different for pre- and post-menopausal women, or, if appropriate, the data can be combined into one model, which describes the change in the bone measurement over age.

3. Reproducibility Studies

These studies define the clinical precision of the device. They can also provide the basis for a claim of monitoring a patient over time or monitoring a patient under therapy, when precision is combined with the expected change in the patient's measurement over a given time interval. Reproducibility needs to be established with respect to measurement-to-measurement, device-to-device, and operator-to-operator variability.

The description of variability (operator-to-operator and device-to-device) studies should include methods, raw data, and statistically valid analyses. They should include both phantom and clinical studies or an explanation why one or the other is not required.

In order to estimate the repositioning, inter-operator, and device-to-device variability for the ultrasound measurements, you should use at least 3 operators and 3 devices and the study should be performed on at least 6 pre-menopausal Caucasian women (20 to

45 years of age) and at least 6 post-menopausal Caucasian women (aged 55 to 80 years). Subjects should be distributed throughout each of these age ranges. Each subject should be measured in duplicate (with repositioning between measurements) by each combination of operators and devices, unless you can propose a more efficient design. You can present your study design to the Agency for review if desired.

The results should be analyzed separately for each of the two age groupings (below 45 and above 55) to obtain the variance components for operator, device, and repositioning, as well as, the combined variability. These in turn should be used to obtain the corresponding coefficients of variation. If the results can be demonstrated to be combinable across age groupings, then all the data can be pooled. The combined variability should also be presented as a fraction of the standard deviation of the young normal reference group (or TSD). The T-score of an individual +/- 2 TSD would provide an approximate 95% Confidence Interval on the measured T-score. [Note: If you want to make a monitoring claim, you will need to specify the frequency of monitoring and show that the overall precision of the device measurement allows for such a claim over a specified time interval.]

4. Fracture Risk Study

The effectiveness of the bone sonometers should be based on the ability to assist in:

- the prediction of risk of atraumatic fractures in the elderly,
- the diagnosis of osteoporosis, and
- possibly the detection of diseases involving non-age-related bone loss.

You should provide a detailed study protocol and present the raw data and all details of the statistical analyses. The study can be performed retrospectively or prospectively.

a) Retrospective Fracture Risk Study

The retrospective fracture risk study should be controlled with each subject being assessed by the test device and an acceptable control device (either an approved ultrasound or x-ray device) that preferably, but not necessarily, measures the subject in the same anatomical area. A potential difficulty with a non-randomized retrospective study is that it may be difficult to determine the amount of bias that is introduced because the subjects are not prospectively followed. The use of a concurrent control will allow for the assessment of some of this bias. All women in the study should be between 60 and 80 years of age and approximately half of them should have had recent (within the past 3 years) atraumatic fractures of the hip, spine and/or wrist, as determined by radiographs or some other reliable method of assessment. A sample size of 240 women should be adequate to show whether the device has the ability to discriminate between women who have and have not experienced atraumatic fractures in the past. Statistical procedures such as age-adjusted logistic regression or age-matched ROC curves should be adequate to demonstrate this ability.

b) Prospective Fracture Risk Study

You may perform a prospective study that will demonstrate the ability of the device to assess fracture risk. The study should be able to evaluate the device's ability to distinguish women, of the same age and ethnicity, who do and do not suffer an atraumatic fracture during the time interval of the study, perhaps 2 or 3 years. This discriminatory ability can be expressed as the area under the ROC curve (AUC). The study should be sized such that the AUC adjusted for age has an acceptable 95% confidence interval. Subjects should be of sufficient age that there is a reasonable likelihood that some will experience fractures during the study. If you intend to do a prospective fracture risk study we recommend that you submit your proposed study design to the Agency for review before commencing the study.

E. Labeling (see http://www.fda.gov/cdrh/ode/labeling.pdf)

The device labeling should contain the following:

1. Manufacturer's name, device name and model

2. Date of the labeling (or revision)

3. Essential Prescribing Information (This is a summary of the complete labeling.)

   a) Device description
   Include appropriate information, such as anatomical site(s) scanned, major components of system, ultrasound parameter being used, and scanning method.

   b) Indications for use
   Should be identical to that given in section IV.A above.

   c) Contraindications
   Generally, there will be none.

   d) Warnings and precautions
   Include information that should be followed for safe use. This should not be an exhaustive list of warnings, but should be limited to those that have severe consequences and are specific to this device. They should be categorized into General, Clinical, etc. and should include the following:
   - Warn against the use of gender- and ethnic-specific normative data for fracture risk assessment. The labeling should emphasize the need to use the same healthy young Caucasian female database for calculation of every patient's T-score, regardless of her/his gender and ethnicity.
   - Recommend methods for preparing the skin (e.g. cleaning with alcohol pads) and ensuring good coupling between the ultrasound transducer and the skin

surface (e.g. use of coupling gel for dry systems and eliminating bubbles for wet systems).

- Warn against measuring patients with non-intact skin.
- Warn against the use of different calibration phantoms in serial patient studies.
- Provide the maximum period of time over which recommended phantoms or test objects should be assumed to be reliable.

e) Adverse events

Describe possible undesirable effects associated with the use of this device and serious events that occur with such frequency that the clinician needs to be warned. Generally, there will be none.

f) Individualization of Treatment

A statement should be included to obviate any assumption by the user that use of the device is restricted to the diagnosis of osteoporosis and estimation of fracture risk in Caucasian women only. For example: "This device may be used to diagnose osteoporosis and to estimate fracture risk in men and in women of ethnicity other than Caucasian, and is not restricted to Caucasian women, though the same young normal Caucasian female database needs to be used to calculate the T-score for all patients, regardless of gender and ethnicity."

A statement should also be included such as, "There are similarly no gender or ethnic restrictions on its use in monitoring bone changes over time or assessing non-age-related bone loss, though for the latter assessment, databases need to be employed that are matched to the patient's gender and ethnicity, as well as age."

g) Clinical studies

Information in this section should include a brief summary--a self-contained description of the design, conduct, and most important results of the clinical studies conducted in support of this labeling. It should include the following:

A brief introductory section including

- purpose of the study: be specific, the purpose is to support the indicated use, not to show that the device is "safe and effective";
- study design: e.g., "A multicenter, double-blind comparison of…" One or two sentences should suffice;
- primary endpoints

Patients studied: number of patients in each group, gender, ethnic origin, disease category, age range principal and unusual inclusion and exclusion criteria.

Methods: a concise statement of the methodology involved in gathering the primary effectiveness and safety data; and

Results: effectiveness and safety, usually summarized in a table entitled, e.g., *Principal Effectiveness and Safety Results*. Avoid promotional prose. Avoid use

of the words "safe" and "effective" in the description of the study and results, except as suggested for the table title.

h) Prescription legend
Bone sonometers are prescription devices and are misbranded if their labeling does not bear the following statement or allowed alternatives (see (http://www.fda.gov/cdrh/comp/rxlabeling.html):

Caution: Federal Law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

5. Complete user manual, technical manuals, and other labeling

a) Physician information
Provide physician labeling that discusses osteoporosis, the different methods of measuring bone strength, the error and precision of these measurements, the interpretation of results, etc., (e.g., differences in patient classification are possible for two different methods). Provide a discussion of the precision of the device and the proper use of the device if used for monitoring patients under treatment (e.g., the appropriate monitoring interval). You should also provide references to the papers on the differences of results from the various bone densitometers and sonometers.

b) Provide detailed instructions for cleaning and disinfecting the device between patients. Include a list of any accessories needed to clean and disinfect the device and the chemical name of the recommended germicide.

c) A recommended quality assurance program for the user that assures the continued proper operation and calibration of the device. Describe conditions (e.g., duration of use, component replacement, quality control and calibration procedures) that must be managed during normal use to maintain the safety and effectiveness of the device.

6. Patient counseling information

Provide labeling in a form that the practitioner can provide to patients that describes osteoporosis, explains why the disease is of concern to women, explains the measurement of bone using ultrasound and indicates that ultrasound measurements are different from x-ray bone densitometry (e.g., How does it work? What will it tell me? Why is this important? What other tests are available and how does your device differ? What should the patient know?). This includes information for the clinician to counsel patients and, if necessary, guidelines on informed consent. (see http://www.fda.gov/cdrh/ohip/guidance/1128.html)