

# **Guidance for Industry and FDA Staff**

---

## **Class II Special Controls Guidance Document: Bone Sonometers**

**Document issued: July 17, 2008**

**The draft of this document was issued February 15, 2006.**

**This document supersedes Bone Sonometer PMA Applications;  
Final Guidance for Industry and FDA, issued June 21, 2001.**

For questions regarding this document, contact Robert A. Phillips at the Center for Devices and Radiological Health (CDRH) at 240-276-3666, or at [roberta.phillips@fda.hhs.gov](mailto:roberta.phillips@fda.hhs.gov).



**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Devices and Radiological Health**

**Radiological Devices Branch  
Division of Reproductive, Abdominal, and Radiological Devices  
Office of Device Evaluation  
and  
Division of Imaging and Applied Mathematics  
Office of Science and Engineering Laboratories**

# **Preface**

## **Public Comment**

Written 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. Alternatively, electronic comments may be submitted to <http://www.regulations.gov> . 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.

## **Additional Copies**

Additional copies are available from the Internet at: <http://www.fda.gov/cdrh/ode/guidance/1547.html>. You may send an e-mail request to [dsmica@fda.hhs.gov](mailto:dsmica@fda.hhs.gov) to receive an electronic copy of the guidance or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number 1547 to identify the guidance you are requesting.

**TABLE OF CONTENTS**

<b>1. INTRODUCTION</b>	<b>1</b>
<i>The Least Burdensome Approach</i>	1
<b>2. BACKGROUND</b>	<b>2</b>
<b>3. THE CONTENT AND FORMAT OF AN ABBREVIATED 510(K) SUBMISSION</b>	<b>2</b>
<b>4. SCOPE</b>	<b>5</b>
<b>5. DEVICE DESCRIPTION</b>	<b>5</b>
<b>6. RISKS TO HEALTH</b>	<b>7</b>
<i>Identified Risk</i>	7
<b>7. ELECTRICAL SAFETY</b>	<b>8</b>
<b>8. ELECTROMAGNETIC COMPATIBILITY</b>	<b>8</b>
<b>9. ACOUSTIC INTENSITY</b>	<b>9</b>
<b>10. NON-CLINICAL TESTING</b>	<b>9</b>
<b>11. CLINICAL INFORMATION</b>	<b>10</b>
<b>12. LABELING</b>	<b>14</b>

# Guidance for Industry and FDA Staff

---

## Class II Special Controls Guidance Document: Bone Sonometers

*This guidance represents the Food and Drug Administration's (FDA'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 FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance document. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance document.*

### 1. Introduction

This guidance document is a special controls guidance to support the reclassification of bone sonometers into class II (special controls). Bone sonometers are intended to transmit ultrasound energy into the human body to measure the acoustic properties of bone that indicate overall bone health. This guidance is issued in conjunction with a *Federal Register* announcement of a final rule reclassifying bone sonometers.

Following the effective date of a final rule reclassifying the device, any firm submitting a premarket notification submission (510(k)) for a bone sonometer will need to address the issues covered in this special controls guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

This document supersedes the guidance entitled **Bone Sonometer PMA Applications**, issued June 21, 2001.<sup>1</sup>

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

### The Least Burdensome Approach

The issues identified in this guidance document represent those we believe need to be addressed before your device can be approved for marketing. In developing the guidance, we carefully

---

<sup>1</sup> <http://www.fda.gov/cdrh/ode/guidance/1377.html>

## *Contains Nonbinding Recommendations*

considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe there is a less burdensome way to address the issues, you should follow the procedures outlined in the document **A Suggested Approach to Resolving Least Burdensome Issues**, available on the Internet at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>.

## **2. Background**

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of bone sonometers. Thus, a manufacturer who intends to market a device of this generic type must (1) conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E; (2) address the specific risks to health associated with bone sonometers identified in this guidance; and (3) obtain a substantial equivalence determination from FDA prior to marketing the device. (See also 21 CFR 807.85.)

This special controls guidance document identifies the classification regulation and product code for the bone sonometer (refer to **Section 4. Scope**). In addition, other sections of this special controls guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these bone sonometers and lead to a timely 510(k) review. This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87 and the guidance, **Format for Traditional and Abbreviated 510(k)s**<sup>2</sup> and the section of CDRH's Device Advice, **How to Prepare a 510(k) Submission**.<sup>3</sup>

As described in the guidance entitled, **The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**,<sup>4</sup> a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA issues a class II special controls guidance document. Manufacturers considering certain modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

## **3. The Content and Format of an Abbreviated 510(k) Submission**

---

<sup>2</sup> <http://www.fda.gov/cdrh/ode/guidance/1567.html>.

<sup>3</sup> <http://www.fda.gov/cdrh/devadvice/314.html>.

<sup>4</sup> <http://www.fda.gov/cdrh/ode/parad510.html>.

## *Contains Nonbinding Recommendations*

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this special controls guidance document was used during the device development and testing and should briefly describe the methods or tests used. We recommend that you also include a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of Section 807.87 and other items that we recommend you include in an Abbreviated 510(k).

### **Coversheet**

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this special controls guidance document.

### **Proposed Labeling**

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to **Section 12. Labeling** for specific information to include in the labeling for devices of the type covered by this guidance document.)

### **Summary Report**

We recommend that the summary report contain:

#### **Description of the Device and Its Intended Use**

We recommend that you include the performance specifications and, when appropriate, detailed, labeled drawings of the device. (Refer to **Section 5. Device Description** for specific information.) You should also submit an “indications for use” enclosure.<sup>5</sup>

#### **Description of Device Design Requirements**

We recommend that you include a brief description of the device design requirements.

#### **Identification of the Risk Analysis Method**

We recommend that you identify the risk analysis method(s) you used to assess the risk profile, in general, as well as the specific device’s design and the results of this analysis. (Refer to **Section 6. Risks to Health** for the risks to health generally associated with the use of this device that FDA has identified.)

#### **Discussion of the Device Characteristics**

---

<sup>5</sup> Refer to <http://www.fda.gov/cdrh/ode/indicate.html> for the recommended format.

## *Contains Nonbinding Recommendations*

We recommend that you discuss the device characteristics that address the risks identified in this class II special controls guidance document and any additional risks identified in your risk analysis.

### **Description of the Performance Aspects**

We recommend that you include a brief description of the test method(s) you have used or intend to use to address each performance aspect identified in **Sections 7–10** of this class II special controls guidance document. If you follow a suggested test method, you may cite the method rather than describe it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.<sup>6</sup> (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

### **Reliance on Standards**

If any part of the device design or testing relies on a recognized standard, we recommend that you include either:

- a statement that testing will be conducted and meet specified acceptance criteria before the device is marketed; or
- a declaration of conformity to the standard.<sup>7</sup>

Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to Section 514(c)(1)(B) of the Act and the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**.<sup>8</sup>

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any

---

<sup>6</sup> If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

<sup>7</sup> See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions), <http://www.fda.gov/cdrh/ode/reqrecstand.html>.

<sup>8</sup> <http://www.fda.gov/cdrh/ode/guidance/1131.html>.

## *Contains Nonbinding Recommendations*

additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you may submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering certain modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a premarket notification submission for a bone sonometer.

### **4. Scope**

The scope of this document is limited to the device described below.<sup>9</sup>

<b>Procode</b>	<b>Common Name</b>
MUA (21 CFR 892.1180, class II)	Bone sonometer

A bone sonometer is a device that transmits ultrasound energy into the human body to measure acoustic properties of bone. The primary components of the device are:

- voltage generator;
- transmitting transducer;
- receiving transducer; and
- hardware and software for reception and processing of the received ultrasonic signal.

This guidance addresses the following indications:

- determining the possible presence of osteoporosis; and
- assessing bone loss not related to aging.

### **5. Device Description**

We recommend that you identify your device, by the regulation and product code described in section 4. **Scope**, and provide the information discussed below.

#### **Sonometer**

We recommend that you provide a complete description of the device, including:

---

<sup>9</sup> See **Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers** at <http://www.fda.gov/cdrh/ode/ulstran.pdf>.

### *Contains Nonbinding Recommendations*

- indications for use;
- physical description of the device, including how transducers are positioned on the body and anatomical site(s) scanned;
- engineering or block diagrams showing the major components;
- block diagram of the data analysis program; and
- calibration standards used (built-in and external).

## **Hardware and Ultrasound Beam Specifications**

We recommend that you provide the following specifications:

- transducer: diameter, resonant frequency, bandwidth, focusing properties;
- transducer piezoelectric material composition;
- A/D converter sampling rate and bit depth; and
- ultrasound beam width and power spectrum.

## **Software**

We recommend that you include the appropriate software documentation as described in the guidance titled, **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices**.<sup>10</sup> As discussed in that guidance, we recommend that you identify the “level of concern” (minor, moderate, or major) associated with your device and provide documentation consistent with that level. Generally, we consider “minor level of concern” appropriate for the bone sonometers addressed in this class II special controls guidance document.

## **Phantoms**

If the device uses phantoms (for example, in quality control or maintenance procedures), we recommend that you discuss the design, including contents, of any phantoms used. We also recommend that you provide a product sheet detailing the technical and descriptive specifications of the phantoms and explain how the phantoms are used.

## **Accessories**

We recommend that you list all accessories you intend to make available for use with your bone sonometer. In addition, for each accessory, we recommend that you provide:

- a complete description, including photographs or drawings;
- construction, including materials;
- any material standards met; and

---

<sup>10</sup> [www.fda.gov/cdrh/ode/guidance/337.html](http://www.fda.gov/cdrh/ode/guidance/337.html).

## Contains Nonbinding Recommendations

- any previous clearance.

If an accessory is exempt from the 510(k) requirements of the act, we recommend that you indicate its classification regulation. If your accessory is not exempt or previously cleared for this use, bundling with your bone sonometer submission may be appropriate. For information about bundling premarket submissions, see the guidance entitled, **Bundling Multiple Devices or Multiple Indications in a Single Submission**.<sup>11</sup>

## 6. Risks to Health

Demonstrating substantial equivalence requires evidence that the device under review is as safe as or safer than the predicate device(s). Assurance of fitness for safe use requires application of a risk management process consistent with accepted practice for medical device development. The process employs risk analysis, evaluation, and control to manage risks. The evidence necessary to demonstrate substantial equivalence is the documented results produced by that process. FDA recognizes that the risk management process of ISO 14971:2007 (**Medical Devices – Application of Risk Management to Medical Devices**) is consistent with accepted practice for medical devices. The detailed information requested in this guidance is based upon application of the risk management principles and practices that are the basis for that standard. The guidance uses the same terminology.

We recommend that you conduct analyses to identify the risks specific to your device, and the analyses not be restricted to individual fault and failure conditions. We also recommend you include all factors related to the design, manufacture, and use of your device that can affect safety and identify significant hazardous situations. FDA recommends you include in your submission the results of your analyses and evidence demonstrating that risks have been effectively managed.

In the table below, FDA has identified the risks to health generally associated with the use of bone sonometers. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. We recommend that you conduct a risk analysis (before submitting your 510(k)), to identify any other risks specific to your device and include the results of this analysis in your 510(k). If you elect to use an alternative approach to address a particular risk identified in this document, or you have identified risks additional to those in this document, then you should provide sufficient detail to support the approach you have used to address that risk.

Identified Risk	Recommended Mitigation Measures (See Guidance Section Below)
Electrical hazards	Section 7. Electrical Safety
Electromagnetic interference	Section 8. Electromagnetic compatibility

<sup>11</sup> <http://www.fda.gov/cdrh/mdufma/guidance/1215.html>.

*Contains Nonbinding Recommendations*

Tissue damage	Section 9. Acoustic Intensity
Patient mismanagement	Section 10. Non-Clinical Testing Section 11. Clinical Testing Section 12. Labeling

## 7. Electrical Safety

We recommend that you evaluate the electrical safety of your device and its ability to function after exposure to environmental handling hazards. We also recommend that you evaluate your device according to one or more of the following standards (or equivalent methods):

- International Electrotechnical Commission (IEC) 60601-1 Medical Electrical Equipment - Part 1: General Requirements for Safety
- Underwriters Laboratory (UL) 2601-1 Amendment 1 Medical Electrical Equipment: General Requirements for Safety
- American National Standards Institute (ANSI)/AAMI ES-1 Safe current limits for electromedical apparatus
- IEC 60529 Degrees of protection provided by enclosures (IP Code) Consolidated Edition
- IEC 60721-4-x TR (Technical Reports).

The features and design of your device will determine which of the above standards or equivalent methods we recommend you use and whether other standards are appropriate in addition to or in place of these.

## 8. Electromagnetic Compatibility

Electromagnetic compatibility (EMC) encompasses both:

- emissions (interference with other electronic devices) and
- immunity (resistance to interference, which is created by emissions from other electronic devices with performance of the device).

We recommend that you evaluate the EMC of your device according to IEC 60601-1-2 Medical Electrical Equipment -- Part 1: General Requirements for Safety; Electromagnetic Compatibility - Requirements and Tests (Second Edition, 2001) or equivalent method.

### **Emissions**

We recommend that EMC testing demonstrates that the device will not adversely interfere with the performance of other electronic devices, such as active implantable devices (e.g., pacemakers, defibrillators). FDA recommends your testing include:

- radio frequency (RF) electromagnetic emissions;

## *Contains Nonbinding Recommendations*

- low frequency magnetic emissions; and
- conducted emissions.

### **Immunity**

We recommend that EMC testing demonstrates that the device will perform as expected in the presence of other electrical and electronic devices or other sources of electromagnetic disturbance (EMD) in the intended environment of use (immunity). We also recommend that the device operates in an acceptable manner (few EMC standards require operation within specification) during and after exposure to various forms of electromagnetic disturbance.

FDA recommends your immunity testing include:

- electrostatic discharge (ESD)
- radiated RF electromagnetic fields
- electrical fast transients and bursts
- surges
- conducted RF electromagnetic energy
- voltage dips, short interruptions, and voltage variations on power supply input lines
- low-frequency magnetic fields
- quasi-static electric fields.

## **9. Acoustic Intensity**

FDA recommends that you measure the bone sonometer's acoustic output intensity. We recommend the description include the average and maximum acoustic intensities measured for the device (e.g.,  $I_{SPPA,3}$ ,  $I_{SPTA,3}$ , MI). See also the guidance entitled **Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers.**<sup>12</sup>

## **10. Non-Clinical Testing**

We recommend that you describe:

- algorithms for computing the measurements (e.g., broadband ultrasonic attenuation (BUA), speed of sound (SOS));
- results of laboratory testing to establish the accuracy and precision of measured values;
- frequency range used in the calculation of attenuation versus frequency (for BUA measurement), including detailed discuss of the algorithm (e.g., log spectral difference, centroid shift);

---

<sup>12</sup> <http://www.fda.gov/cdrh/ode/ulstran.pdf>.

### *Contains Nonbinding Recommendations*

- specification of 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, threshold value);
- purposes and implementations of any filters applied to the received data;
- procedures and testing performed to validate quality assurance tests;
- analysis of the long-term stability of acoustic properties of test objects;
- validation of your recommended method for cleaning and disinfecting the system between patients; and
- results of laboratory testing to assess the effects of environmental factors, including temperature and line voltage.

## **11. Clinical Information**

In accordance with the Act, the Agency will rely upon well-designed bench and/or animal testing rather than require clinical studies to establish safety and effectiveness for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. While, in general, clinical studies will not be needed for most bone sonometers, FDA may recommend you collect clinical data for a bone sonometer with any one of the following:

- indications for use dissimilar from legally marketed devices of the same type;
- designs dissimilar from legally marketed designs; and
- new technology (i.e., technology different from that used in legally marketed devices of the same type).

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale.

If a clinical study is needed to demonstrate substantial equivalence (i.e., conducted prior to obtaining a 510(k) clearance of the device), the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA believes a bone sonometer addressed by this guidance document is a non-significant risk device. Therefore, the study is subject to the abbreviated requirements of 21 CFR 812.2(b).<sup>13</sup> In addition to the requirements of Section 21 CFR 812.2(b), sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR part 56) and informed consent (21 CFR Part 50).

We recommend you conduct clinical studies for generating reference databases (described below) and assessing reproducibility for all bone sonometers. For these studies, and any other clinical studies you conduct in support of your 510(k), we recommend you provide the information described in this section.

---

<sup>13</sup> See <http://www.fda.gov/oc/ohrt/irbs/devices.html#risk>

## **Study Design**

We recommend you describe the study design in detail, including the number of sites, any randomization, and control arms.

## **Subjects Enrolled**

We recommend that you show the number of subjects enrolled in the study, segregated by:

- gender;
- ethnic origin;
- disease category;
- age range;
- principal inclusion and exclusion criteria; and
- unusual inclusion and exclusion criteria.

## **Methodology**

We recommend you include a detailed description of the methodology you used in gathering clinical data.

## **Exclusion Criteria**

For all the clinical studies described in this guidance, we recommend the exclusion criteria listed below.

### **Current or Recent Use of Bone-Active Drugs**

We recommend that you exclude subjects who have taken the following drugs within a specified interval of time immediately preceding the study. We recommend that you provide justification that the length of the specified interval is sufficient to ensure the effects of using these drugs prior to the specified interval are minimal:

- bisphosphonates;
- calcitonin;
- therapeutic doses (>1000 I.U. daily) of vitamin D;
- estrogens or selective estrogen receptor modulator (SERM);
- therapeutic doses (> 2 mg/day) fluoride;
- teriparatide;
- drugs under research protocols; and
- unstudied or unapproved drugs.

### **Presence of Metabolic Bone Disease**

We recommend that your exclusion criteria include:

- hyperparathyroidism or hypoparathyroidism within 5 years;

### *Contains Nonbinding Recommendations*

- osteitis deformans (Paget's disease of bone);
- renal osteodystrophy; and
- osteomalacia.

#### **Other Diseases or Drugs**

We recommend that your exclusion criteria include:

- gastrointestinal malabsorption;
- liver disorders;
- chronic renal disease;
- unstabilized hyperthyroidism or hypothyroidism;
- hyperadrenocorticism or hypoadrenocorticism;
- concomitant use of oral corticosteroids (any dose);
- use of oral corticosteroids within past 6 months, if less than equivalent of 7.5 mg daily of prednisone, or use of a greater dosage, within the past year;
- use within past 6 months of antiseizure drugs, barbiturates, or anticoagulants; and
- stroke with total or partial paralysis with residual disability lasting more than 3 months.

#### **Diagnostic Measurements**

We recommend that you provide:

- rationales and formulas (such as linear combinations) for indexes that are derived from acoustic measurements;
- description of the algorithms used to calculate the values presented (T-scores, Z-scores, etc.); and
- copies of all pages of test results that are either displayed on a monitor or printed out as hard copy.

#### **Reference Databases**

Reference databases are used to calculate T and Z scores. The T-score expresses a measurement relative to a normal reference database of healthy young Caucasian females. The Z-score expresses a measurement relative to a normal reference database of an individual's peer group. Relative (dimensionless) values like T-scores and Z-scores are often easier to interpret than absolute values of measurements like bone density, broadband ultrasound attenuation, or speed of sound.

#### **T-Score**

## *Contains Nonbinding Recommendations*

The T-score is the patient's measurement minus the average measurement of healthy young (between ages 20 and 39) Caucasian females divided by this group's standard deviation.

We recommend that you 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.<sup>14</sup> We recommend that you use two or more geographically separated sites to assure that the test group is representative.

We recommend that you determine device-specific T-score thresholds. Because of discordance among skeletal sites and technologies, the World Health Organization (WHO) threshold for osteoporosis (T-score  $< -2.5$ )<sup>15</sup>, which was developed for axial dual energy x-ray absorptiometry (DEXA) measurements, may not be appropriate for bone sonometers. We recommend that you include comparison ultrasound and axial DEXA data on the same set of patients to determine the level of discordance.

### **Z-Score**

The Z-score is the patient's measurement minus the average measurement for those in the same age decade, gender, and ethnicity divided by this group's standard deviation. We recommend that you provide gender- and ethnic-specific normative databases, across all ages within the range of interest (generally from 20 to 80 or 90), to facilitate interpretation of bone measurements for evaluating secondary (non-age related) causes of low bone mass.

We recommend that databases for each ethnicity and gender consist of measurement results from at least 50 subjects per institution per decade for the range of decades of interest. We recommend that you use two or more geographically separated sites to assure that the test group is representative. We also recommend that you analyze the databases by decade and present the mean and standard deviation of the appropriate bone sonometer measurement for each decade.

## **Reproducibility Studies**

These studies measure the clinical precision of the device. For all indications, we recommend that you estimate:

- repositioning precision;
- inter-operator reproducibility; and
- inter-device reproducibility.

---

<sup>14</sup> The optimal range is 300 to 500 subjects according to Martin et al., *Normal Values in Clinical Chemistry*, Marcel Dekker, 1975, pages 51–52.

<sup>15</sup> *Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis*, World Health Organization, WHO Technical Report Series 843, 1994.

## *Contains Nonbinding Recommendations*

FDA recommends that you describe your variability studies and include methods and analyses. We also recommend that you provide a brief rationale supporting the statistical validity of your analyses. FDA recommends that your variability studies include both phantom and clinical studies or an explanation why one or the other is not appropriate.

We recommend using the position of the International Society for Clinical Densitometry (Baim et al., *J. Clin. Densitom.*, 8, 371–378, 2005) that the number of subjects in a reproducibility study be 30 in the case of paired measurements or 15 in the case of triplicate measurements. We recommend repositioning of subjects between measurements.

We recommend that you segregate your data into two groups (normal and osteopenic/osteoporotic) and analyze the results separately to obtain:

- variance components for repositioning, operator, and device; and
- combined variability.

We recommend that individuals in each of the two groups exhibit a wide range of bone mineral densities. If you demonstrate the results are combinable across groups, then it is appropriate to pool all the data. We also recommend that you present the combined variability as a fraction of the standard deviation of the young normal reference group or T-score standard deviation (TSD). The T-score of an individual  $\pm 2$  TSD provides an approximate 95% confidence interval on the measured T-score.

We recommend that you measure both short-term (same day) and intermediate-term (different day) precision.

Bone sonometers are generally portable devices that are often used at health fairs and in other settings where environmental conditions may vary considerably. Therefore, we recommend that clinical testing of reproducibility include testing under different environmental conditions so that effects of difference in temperature and line voltage can be assessed.

## **12. Labeling**

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions will assist you in preparing labeling that satisfies the requirements of 21 CFR 807.87(e).<sup>16</sup>

### **Indications for Use**

We recommend that the indications for use specify the target population and include one or more of the following elements:

---

<sup>16</sup> Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of part 801.

## *Contains Nonbinding Recommendations*

- determining the possible presence of osteoporosis and assessing fracture risk;
- assessing bone loss not related to ageing.

For example:

The device performs a quantitative ultrasound measurement of bone. The results 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.

## **Contraindications**

We recommend that the labeling list all contraindications, if any.

## **Warnings**

We recommend that the labeling include warnings against using the device on skin with open wounds or signs of trauma, bleeding, or infection.

## **Directions for Use**

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, we recommend providing clear and concise instructions for professional users that delineate the technological features of the specific device and how the device is to be used on patients. FDA recommends that instructions encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

We recommend that the instructions also include:

- a protocol for cleaning and disinfecting between patients, including a list of any accessories needed to clean and disinfect the device and the chemical name of the recommended germicide;
- methods for preparing the skin (e.g., cleaning with alcohol pads) prior to examination;
- methods for 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);
- recommendations for quality assurance methods; and
- maximum period of time over which phantoms or test objects may be assumed reliable.

We also recommend that the instructions emphasize the need to use the same healthy young Caucasian female database for the calculation of every patient's T-score, regardless of gender and ethnicity. We advise against the use of gender- and ethnic-specific normative data for fracture risk assessment.

## **Device Description**

We recommend that labeling identify the:

- anatomical site(s) scanned;
- major components of system;
- ultrasound parameter(s) being used; and
- scanning method.

## **Precautions**

We recommend that the labeling list possible adverse events associated with the use of this device.

## **Individualization of Treatment**

We recommend that labeling advise users that the device is not limited to use in Caucasian women. For example, “This device may be used to determine the possible presence of osteoporosis and to estimate fracture risk in Caucasian and non-Caucasian men and women. You should use the same young normal Caucasian female database to calculate the T-score for all patients, regardless of gender and ethnicity.”

## **Clinical Studies**

FDA recommends that information in this section include a brief summary; that is, a self-contained description of the design, conduct, and results of the clinical studies for generation of the reference database and assessment of precision. We recommend the summary include the information described below.

### **Study Design**

We recommend that labeling briefly describe the study design in particular by addressing the number of sites, any randomization, control arms, and other important information.

### **Subjects Enrolled**

We recommend that your labeling show the number of subjects enrolled in the study, segregated by:

- gender;
- ethnic origin;
- disease category;
- age range; and
- principal and unusual inclusion and exclusion criteria.

## *Contains Nonbinding Recommendations*

### **Methodology**

We recommend that labeling include a concise statement of the methodology used in gathering the effectiveness and safety data.

## **User Manual, Technical Manual, and Other Labeling**

### **Physician Information**

We recommend that the physician labeling discuss:

- osteoporosis;
- different methods of measuring bone strength;
- error and precision of these measurements;
- interpretation of results (e.g., differences in patient classification are possible for two different methods);
- precision of the device; and
- references to publications on the differences of results from the various bone densitometers and sonometers.

We also recommend that the physician labeling describe a quality assurance program for the user that assures the continued proper operation and calibration of the device. We recommend you include the conditions that should be managed during normal use to maintain the safety and effectiveness of the device, such as:

- duration of use;
- component replacement;
- quality control; and
- calibration procedures.

We recommend that the patient labeling (if provided) explain:

- osteoporosis;
- why the disease is of concern to women; and
- the measurement of bone using ultrasound.

We also recommend that the patient labeling (if provided) explain that ultrasound measurements are different from x-ray bone densitometry, addressing questions such as:

- How does ultrasound measurement work?
- What will it tell me?

*Contains Nonbinding Recommendations*

- Why is this important?
- What other tests are available and how does your device differ?
- What should the patient know?

See also **Guidance on Medical Device Patient Labeling**.<sup>17</sup>

---

<sup>17</sup> <http://www.fda.gov/cdrh/ohip/guidance/1128.html>