SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Ultrasound Bone Sonometer
Device Trade Name:	DTU-one Ultrasound Scanner
Applicant's Name, Address:	Osteometer MediTech, Inc. 12515 Chadron Avenue Hawthorne, CA 90250
PMA Number:	P980010
Date of Good Manufacturing Practice Inspection:	April 22, 1999
Date of notice of approval to the applicant:	September 19, 2000

II. INDICATIONS FOR USE/INTENDED USE

The DTU-one is intended to perform a quantitative ultrasound measurement of the calcaneus (the heel bone) the results of which can be used in conjunction with other clinical risk factors as an aid to the physician in diagnosis of osteoporosis (T-score) and in the determination of fracture risk in men and women. The measurement may also be used in Caucasian women to aid in the detection of medical conditions, other than age-related bone loss, that lead to reduced bone density.

III. DEVICE DESCRIPTION

The DTU-one measures the broadband ultrasound attenuation (BUA in dB/MHz). The parameter output is expressed both as a T-score, for all patients (comparison to a young female Caucasian database) and a Z-score (comparison to age, gender and race specific database), for Caucasian women only—due to the absence of applicable reference databases for other ethnic groups and males.

The scanning method is rectilinear using ultrasonic transducers with a focused beam and bandwidth of 97% (3dB down at 278.1 to 801.9 kHz.), with a scan resolution of 0.6 millimeters over a frequency range of 300 to 650 kHz. The transducers are focused with the focus distance at 33 mm. The center frequency is 540 kHz. The scan time is approx. 3 minutes, using water as a coupling medium. The manufacture of the DTU-one Ultrasound Scanner involves hardware assembly of chassis, power supply, printed circuit boards, power and signal cables, and other components of the device. The operating software is installed/integrated in the hardware and is tested at the systems level on phantoms of known value.

Device Components:

The DTU-one hardware, including accessories, consists of:

- DTU-one Ultrasound Scanner and water container (foot tank)
- Computer and monitor , with the following minimum specifications: Windows NT operating system, 120 MHz clock-rate, 32 MB RAM, and 1 serial and 1 parallel port (e.g.: IBM 330-466DX2 computer and 14L8 15" SVGA monitor. The PC and connected equipment complies with United States FCC rules Part 15 and has the CE mark.
- Printer (optional) e.g.: HP 600 Series (HP 690c)
- DTU-one phantom
- Heel fixation ring

- DTU-one distilled water solution. It is composed of distilled water and a proprietary wetting agent.
- SBR Lipocream.

Cleaning and disinfecting:

The following materials are required for cleaning, disinfecting and maintaining the DTU-one but are not provided by Osteometer MediTech, Inc.: Distilled water, 70% Isopropyl Alcohol, and *5%* Distilled White Vinegar.

Electrical service: 115 VAC, 60 Hz or 230 VAC, 50 Hz.

Environmental conditions: The DTU-one should be placed in an environment where humidity of 10 to 80 % (non-Condensing) and a room temperature of 59 to 86 F (15 to 30 C) can be maintained.

IV. CONTRAINDICATIONS

None known.

V. WARNINGS AND PRECAUTIONS

A. Warnings

The DTU-one is not intended for measurements on patients under 20 years of age, or patients older than 80 years of age. Reference data is not available for patients below 20 or over 80 years of age. Patients matching these criteria will not receive either a T- or Z-score due to the lack of reference data.

The DTU-one must be cleaned and disinfected after each patient. Doing so may help prevent possible transmission of infection between patients.

Do not use the DTU-one on patients with breached skin or open sores on the foot or heel area. Doing so can increase the risk of infection transmission between patients.

Do not operate the DTU-one without first reading the Operator's Manual and the Essential Prescribing Information.

A Quality Control (QC) phantom measurement procedure should be performed every day before patient measurements. If the procedure fails twice, contact your Osteometer MediTech representative or the Osteometer MediTech Service Department for assistance.

Only trained technicians should operate the DTU-one.

B. Precautions

A component of the DTU-one Solution may cause a sensitization reaction in some patients.

Wear protective gloves when cleaning the DTU-one.

Soiled material should be disposed of in appropriate waste receptacles.

Use 70% alcohol in a well ventilated area away from open flame or sparks.

Do not attempt any repairs—there are no user-serviceable parts.

Do not expose the computer to liquids or moisture.

Do not put any electric or battery-operated device in the heel bath.

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VI. ALTERNATIVE PRACTICES AND PROCEDURES

Besides the technology used in the Osteometer MediTech DTU-one Ultrasound System and other ultrasound systems, fracture risk can be estimated by X-Ray Densitometry and Quantitative Computed Tomography (QCT).

X-Ray Densitometry: These radiological technologies include single photon absorptiometry (SPA), single x-ray photon Absorptiometry (SXA), dual photon absorptiometry (DPA), and dual x-ray photon absorptiometry (DEXA). These technologies measure the attenuation of a beam of ionizing radiation passing through the wrist, forearm, calcaneus, hip, or spine, etc. to estimate the bone mineral density.

Quantitative computed tomography (QCT): QCT used computed tomographic cross-sectional reconstruction methods, derived from scanning an x-ray beam across the body, to estimate the bone mineral density in a specific piece of bone.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

No adverse reactions or deaths were reported in the clinical studies. There have been no reported adverse events associated with the use of, or operation of, the DTU-one Ultrasound Scanner.

VIII. PRE-CLINICAL STUDIES

A. Physics

Ultrasound output power was measured to be $I_{spta.3}$= 0.048 W/cm^2 and $I_{sppa.3}$= 0.521 W/cm^2, which are well below acceptable pre-amendment acoustic output levels for the heel.

B. Electromagnetic Compatibility

The DTU-one was tested for its EMC immunity and emission properties. The EMC testing was conducted according to the requirements stated in Council Directive 93/42/EEC relating to electromagnetic compatibility.

Tests were performed according to the standard EN 60601-1-2, May 1993, also including the test conditions specified in EN 55011, Class B, IEC 801-3/1984, EN 61000-4-4 / IEC 1000-4-4 / IEC 801-4, IEC 801-2/1991 and IEC TC 65(Sec.) 137 / DS 5103. Testing confirmed that the DTU-one meets all referenced standards for electromagnetic compatibility. The PC system was not tested as part of the system, but must be CE marked and thereby comply with EMC directive 89/336/EEC. The PC used in the test was an IBM 330-466DX2, which holds the CE-mark and consequently complies with 89/336/EEC. The system also complies with United States FCC Rules, Part 15.

C. Electrical Safety

The device consists of plastic and metal housing of mechanical, electrical and electronic components. Specific internal components include transducers, motor, computer and software, power supply, and a transducer driver.

The device conforms to UL 2601-1, Medical Electric General Requirements for Safety, EN 60601-1-1 and EN 60601-1 with A1, A2, A12 and A13 (A2 except § 52.1). Testing confirmed that this device meets all referenced standards for electrical safety. The connected PC system must be located outside the patient vicinity (more than 6 feet away) and must be CE marked and thereby comply with the European Safety Norm EN 60601-1-1 as well as US Standards UL 2601-1-1.

The system will at all times be installed by a technician certified by Osteometer MediTech, Inc. to ensure that all standards regarding electrical safety are met. The specific instructions are listed in the technical manual which is presented to the technician as part of the certification process.

D. Software

A software verification protocol used to test the DTU-one software was submitted by Osteometer and found to be adequate. A hazard analysis indicated that all software and hardware patient and user concerns were adequately addressed. Verification, validation and unit testing demonstrated the device would operate in a manner as described in the specifications.

E. Cleaning and Disinfection

Recommendations on cleaning and disinfection are provided in the Operator's Manual. The device is intended to be used only on intact skin, and the disinfectant used for cleaning is 70% isopropyl alcohol.

F. Biocompatibility

The materials that come in contact with the patient are distilled water with DTU-one solution, SBR-Lipocream™, and the heel and toe fixation ring. The polyurethane water and heel ring are in the heel bath and the Lipocream is applied to the foot before it is placed in the heel bath. Lipocream is marketed over-the-counter as a consumer cosmetic. Polyurethane is used in many medical devices. Review of the product safety sheets for the constituents of these items indicates that they are compatible for intact skin contact. A component of the DTU-one Solution may cause a sensitization reaction in some patients

IX. SUMMARY OF CLINICAL STUDIES

A. Objectives

Clinical studies were conducted to assess the safety and effectiveness of the DTU-one Ultrasound Scanner as an aid in establishing the diagnosis of osteoporosis and assessing risk of osteoporotic fracture. The primary objectives of these studies were to:

1. assess fracture risk;
2. establish a US reference database; and
3. assess precision.

B. Clinical Trials

1. General criteria for patient selection, inclusion and exclusion

Inclusion criteria:

a. aged 20 years and above;
b. in good general health without serious acute or chronic diseases; and
c. who were informed orally and in writing and who signed an informed consent form.

Exclusion criteria:

a. pregnancy;
b. long-term immobilization , or >= 2 months within the last 6 months;
c. medical treatment within the last 6 months, or chronic long-term treatment ever with one of the following compounds: androgens, calcitonin, cortico-steroids (systemic), vitamin D (exception: multivitamin tablets), medication for epilepsy, thyroid hormones and anti-thyroid treatments except the symptomatic use of topical steroids;
d. hormonal replacement therapy (HRT) (systemic) within the last 2 years;
e. treatment with fluoride, bisphosphonates, insulin, or peroral antidiabetic medicines;
f. known or suspected premalignant or malignant conditions or anamnesis of malignant diseases except from basal cell carcinoma and conization after having a smear test showing abnormal cells, succeeded by a normal smear test; and
g. serious systemic disease, which potentially could disturb the study, or the interpretation of the results from the study.

2. Fracture Risk Study

a. Patient Selection

The fracture study included normal Danish women, 20 years and older, and Danish women with osteoporotic fractures. Spinal fracture status was evaluated according to the method developed by Genant et al.[1] Hip fracture status was assessed by radiological verification. Inclusion/Exclusion criteria are listed above.

The fracture study was carried out in Denmark at two different centers [Center for Clinical & Basic Research (CCBR), Aalborg, and Bispebjerg Hospital, Copenhagen].

b. Experimental design

Two studies were done, involving successive bone measurements on each subject by the DTU-one Quantitative Ultrasound (QUS) device and a DEXA X-ray Bone Density measurement device. The results were analyzed for the fracture risk assessment capability of the DTU-one. Analysis of DEXA results was performed to allow assessment of possible study bias. In both studies, there were two groups of women, one group who had experienced osteoporotic fractures and one group who had not.

For one study, the fractures were hip fractures due to falls, and the control group was an age-matched set of women who had experienced falls without fracture. The other study involved women with x-ray-confirmed spinal fractures, compared to a control group of age-matched women without such fractures.

The data from each device were converted to T-scores, and analyzed by use of ROC curves to evaluate the devices' ability to predict the presence of fracture due to reduced bone density. The two studies differed somewhat in the types of groups compared, and each study is briefly described below.

The first study conducted at the Center for Clinical & Basic Research (CCBR), Denmark, used data to compare calcaneus (heel) DTU-one measurements of BUA to DEXA measurements in two groups of women. The original study, as described in the protocol, was conducted to ascertain age-related longitudinal changes in both DEXA measurements and morphology of the vertebrae in women and men, and to compare these changes to the age-related changes in bone mineral density in the rest of the skeleton as well as morphology of spine determined by conventional x-ray.

Both DEXA and conventional x-rays were used to get as much information about the patients' bones as possible.

Ultrasound assessment was added to the original protocol before the study began. Initially 400 men and 400 women were entered into this study, age 20 years and above. A subgroup of individuals over the age of 50 years received x-rays of the spine.

The subgroup consisted of 179 men and women; however, data are reported from the 112 subject female subgroup. Of this set of data, 58 women were identified who experienced vertebral fractures over the course of the study. From those other participants who did not experience spinal fractures, all 54 age-women were included. These data were analyzed to assess the ability of the DTU-one T-scores to differentiate the fracture from the non-fracture groups.

The second study, 48 subjects, was conducted at Bispebjerg Hospital, Copenhagen, Denmark. The study included the following number of patients in two groups: 1) Twenty-five postmenopausal women with a recent hip fracture due to a fall. Patients were scanned as soon as possible after the occurrence of the fracture (median: 10 days) to avoid the influence of bone loss due to immobilization after the fracture. 2) Twenty-three women who had fallen, but with no fracture of any sort occurring, were age matched with the first group.

For the DEXA hip scanning, the DPX-IQ from Lunar Corporation, Madison, WI was used, and the reference figures provided by Lunar Corporation were used.

c. Data analysis

Logistic regression analysis and analysis of the Area Under the Receiver Operating Characteristic (ROC) Curves were performed on the data. The logistic analyses were adjusted for age since age is a important predictor for fracture risk

The statistical procedures used for computation of the ROC curves, the areas under the curves, and the difference in the curve AUC's were those based on the Hanley-McNeil methods. The software MEDCALC was employed to draw the ROC curves and produce the statistical confidence intervals and tests of significant differences in AUC. These ROC analyses were not adjusted for the effect of age.

The results from the MEDCALC system for the two studies are listed below.

CCBR Study of Spinal Fracture
58 Spinal Fractures and 54 No-fracture Controls

DTU-one BUA (Left Heel)		DEXA BMD (Forearm)		DEXA BMD (Spine)		DEXA BMD (Femoral Neck)		DEXA BMD (Total Femur)	
AUC	SE	AUC	SE	AUC	SE	AUC	SE	AUC	SE
0.713	0.049	0.662	0.051	0.668	0.051	0.622	0.053	0.652	0.052

Bispebjerg Study of Falls, With Hip and Without Any Fracture
23 Falls with Hip Fracture and 21 Falls-without-Fracture Controls

DTU-one BUA (Right Heel)		DTU-one BUA (Left Heel)		DEXA BMD (Forearm)		(Lunar) DEXA BMD (Femoral Neck)		(Lunar) DEXA BMD (Total Femur)	
AUC	SE	AUC	SE	AUC	SE	AUC	SE	AUC	SE
0.684	0.079	0.650	0.082	0.688	0.079	0.802	0.073	0.759	0.080

In order to assess the sampling variability of the ROC AUC's from the two fracture risk studies, a resampling bootstrap program was written to examine the behavior of the individual AUC's and the results agreed with the Hanley-McNeil results.[2]

d. Results

The logistic regression analyses on the CCBR study data, as well as, the data from the combined studies showed that the device demonstrated with statistical significance (p=0.0015) the ability to distinguish between fractured and non-fractured subjects. The Bispebjerg study was too small to obtain meaningful results.

The ROC curve plots and statistical analyses of the equivalence of the AUCs of the paired ROC curves have been elaborated. For the first study from CCBR there were no significant differences detected between the DEXA and DTU-one discriminating ROC curves. For the second study, from Bispebjerg Hospital, comparing the ability to discriminate fracture from non-fracture status of women who experienced a fall, there were again no statistically significant differences noted between the DTU-one and DEXA measurements in the forearm, or between the DTU-one and the Lunar DPXIQ hip DEXA measurements. Since there was small statistical power in this comparison due to low sample sizes, a third comparison was made by combining the two studies for DTU-one and forearm DEXA BMD measurements, which were common to the two studies. This larger data set, which provided additional statistical power, also showed no statistical difference between DEXA and Ultrasound techniques in their ability to assess fracture status.

3. US Reference Database Study

a. Criteria for patient selection, inclusion and exclusion

For the reference data base, normal American female Caucasians were included, ranging in age from 20-80 years. The reference database study was executed in the states of California, Texas, Nebraska and Pennsylvania. See inclusion/exclusion criteria above.

b. Experimental design

Subjects received a medical history, physical examination including registration of signs and symptoms of osteoporosis, blood pressure and heart rate, height, weight and medicine intake. They then received a measurement of the calcaneus on the left and right foot using the DTU-One following standard procedures.

c. Statistical analysis:

Resulting from this analysis, either decade-specific or age-specific reference ranges were programmed into the DTU-one for use in the ensuing studies. Choice between these two options depended on the functional goodness-of-fit of the model, and an assessment of what, if any, clinical benefit would accrue from dividing the reference range by year instead of decade.

Based on the summary, the mean and standard deviation from the age of 20 to the age of 80 was entered into the reference database for the DTU-one.

The statistical method used to develop the US Caucasian female reference database formed the basis for any user to customize a local reference database.

All data from persons satisfying the criteria (normal US female Caucasians) as stated in the protocols were included in the calculation without removal of outliers. The parameters of interest for the reference population are left and right BUA. The following description represents both parameters.

Visual examination of the data revealed whether a single quadratic (forced monotonic) could be used to fit the reference curve, or if a spline of a linear fit up to age 50 followed by a negative slope quadratic was necessary.

To test for statistical difference between left and right BUA, data from the left calcaneus were compared to data from the right calcaneus. The mean values of BUA were calculated and the differences between left/right and mean values were statistically tested according to a paired t-test. A statistically significant difference was found. Therefore the mean value of BUA was used.

Data from the reference-range-by-age study were plotted in a standard scatter plot with age as the X variable and appropriate DTU-one variable (BUA, mean value of left and right) as Y.

For BUA, it was assumed that there would be a gradual (and probably non linear) decrease in the measurements with increasing age after approximately age 50 (general onset of menopause). The data were visually examined to estimate the functional form of the model to be used to represent the data. Prior experience with the device in the clinical setting in other countries has shown that there is generally no age effect on BUA up to the age of 50, with a quadratic decay in the mean value up to age 80 in females.

In addition to the continuous curve fit, data were segregated by decade and the reference ranges estimated for each decade separately (and tested for significant differences in mean and median value by ANOVA and Kruskal-Wallis).

d. Data analysis

For each subject, the means and standard deviations of the calcaneus measurements by decade by study site were calculated, and then pooled across all sites. Poolability of the study across sites was ascertained by performing a series of one-way Analyses of Variance (ANOVAs) within each age decade to determine if there existed evidence of site differences. A critical value for the F-test for differences between sites was set at 0.01 (to adjust for multiple testing), and no significant differences were noted. In fact, none of the p-values for the F-test was below 0.05.

In order to ascertain if separate values were required for the left and right calcaneus for the DTU-one variable, the data were first visually examined by way of a scatterplot of the left heel values against the paired right heel values in the same individual. The following regression results from this data, showing a correlation coefficient of 0.9244, a slope of 0.92 and an intercept of +4.34. Further examination of this data was performed with the use of Bland-Altman plots, plotting the difference between the paired left and right heel values against the average of the two. In this case there was no apparent relationship between the differences and the level of the measured variable, so the differences observed were tested with a paired t-test. The statistical analysis showed a statistically significant difference between the left and right calcaneus for BUA ($p<0.001$).The individual aggregate % differences from the means of the left and right calcaneus measurements show a necessary adjustment to the calculations for BUA of -0.6 % for the right calcaneus, and +0.6 % for the left calcaneus. Subsequent analyses of the dependence of BUA on age employed the mean BUAs, which were adjusted for the required left and right calcaneus differences.

When a regression analysis of the effect of subject age on BUA from the DTU-one over the range of 20 to 50 years old was performed, no apparent differences were noted in BUA over this age range (slope very close to 0.0). Mean BUA data plotted against age for subjects from 51 to 80 years of age, along with the quadratic polynomial least squares fitted model for data on BUA in this age range showed that a curvilinear decrease in BUA values in this range of ages is evident. SAS results of the quadratic model fit for this data, along with the resulting coefficients, were used to create the age-specific predicted values for BUA. The final model for DTU-one BUA reference range consists of the spline of the linear fit (from ages 20-50) and the quadratic model fit from ages 51 to 80. The fitted spline was employed to create a 95 % tolerance interval around the merged model to create the age-specific reference range for mean BUA.

After these calculations were performed for the mean of the left and right calcaneus DTU-one BUA values, the adjustments for the differences previously noted were made to the data to obtain specific DTU-one BUA reference intervals (by age) separately for the left and right calcaneus application of the device, which were then placed into the software of the DTU-one for the ensuing clinical studies.

e. Results

The results for the left and right calcaneal BUA were obtained from the results of a quadratic regression model for the combined left and right calcaneal BUA as a function of age. For the age group 20-50 years, 217 observations were used to derive the mean value (MBUA) and standard deviation. For the age group 51-80 years, 169 observations were used to derive the following quadratic regression equation to estimate mean BUA (MBUA) at each age:

MBUA (mean of left and right): $34.1648 + \text{Age} \times 0.77948 - (\text{Age}^2 \times 0.00933)$

The mean values for the left calcaneus for ages 20-80 were derived from the following equation:

Left = MBUA + 0.6% of MBUA.

The mean values for the right calcaneus for ages 20-80 were derived from the following equation.

Right = MBUA - 0.6% of MBUA.

Female, left calcaneus, BUA:

The following table shows the mean values of the estimated BUA in the left calcaneus of the reference population over the range of 20 to 80 years of age.

The following data (identified as: "USA Caucasian 1998") will be entered into an existing directory of the DTU-one software program resident on the hard drive under an entry, entitled "Female, left BUA":

20-50 years:	Mean value: 50.13	SD: 6.52
SD for 51-80 years: 7.77		

Female, right calcaneus, BUA:

The following table shows the mean value of the estimated broadband ultrasound attenuation in the right calcaneus of the reference population over the range of 20 to 80 years of age.

The following data (identified as: "USA Caucasian 1998") will be entered into an existing directory of the DTU-one software program resident on the hard drive under an entry, entitled "Female, right BUA":

20-50 years:	Mean value: 49.53	SD: 6.52
SD for 51-80: 7.77		

4. Precision Study

For the precision study, normal Caucasian females were included, ranging in age from 30-90 years, and osteoporotic Caucasian females were included, where osteoporosis is defined as having a femoral BMC or BMD result of at least 2.5 standard deviations below the young normal Caucasian adult female mean value. See inclusion/exclusion criteria listed above.

The Precision Study was executed in the states of California and Missouri, and in Denmark.

a. Experimental design

BUA was measured in the left heel in a total of 99 normal and osteoporotic individuals, three times (and in eight cases only two times), each with repositioning before each measurement, to estimate the precision error of the DTU-one device.

b. Data collection

The data were analyzed separately for each site. The pooled within-subject standard deviation was calculated for each group, and used as a "yardstick" for assessing the data from the correlation study, as well as establishing the precision performance of the measured variable of BUA.

The confidence interval calculations were based on the formulas found in Glüer et al.[3]

For each individual the precision estimates for BUA of the left foot were computed using the means procedure of the SAS System (SAS Institute Inc., Cary, NC USA, Software Release 6.04).

The precision error in each individual was calculated as the coefficient of variation (CV%) by dividing the standard deviation (SD) by the mean value of the three repeated measurements. The overall CV% was obtained by calculating the pooled within-subject standard deviation (root-mean-square deviation), and dividing by the grand mean. For T-Scores computed from these BUA measurements, the observed pooled within-subject standard deviation of the replicate T-Scores was 0.17.

The results of the precision study are presented below as the pooled within-subject CV% and its 95% confidence interval.

c. Results

The in vivo precision error for BUA, for repositioning only, was found to be

Precision error BUA: 2.4%	95% Confidence Interval: 2.13-2.66%

The results given above will appear on the computer screen, printed patient report, and in the DTU-one promotional material which is going to be used in the United States. The standard deviation of the T-score (TSD) is equal to the variability due to repositioning divided by the standard deviation of the young healthy group or 0.177 (of a T-score unit).

X. CONCLUSIONS

A. Fracture Risk Study:

The part of the clinical study that evaluated a total of 160 patients showed by use of logistic regression analysis that the DTU-one is capable of discriminating between patients with hip or spine fractures from those without atraumatic fracture.

B. US Reference Database Study:

The reference data base is representative of a young healthy adult Caucasian female population, suitable for the calculation of T-scores and an older adult Caucasian female population, suitable for the calculation of Z-scores.

C. Precision Study:

The precision study, involving 99 normal and osteoporotic women, yielded a T-score standard deviation (TSD) of 0.177. The precision was obtained through repeated positioning after each measurement.

XI. FDA DECISION:

FDA issued an approval order on September 19, 2000.

The applicant's manufacturing and control facilities were inspected April 22,1999, and the facilities were found to be in compliance with the Good Manufacturing Practices (GMP) regulation.

XII. APPROVAL SPECIFICATIONS:

Directions for use: See attached labeling.

Warnings, Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, and Precautions.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Postapproval requirements and restrictions: See Approval Order.

[1] Genant HK, Wu C, van Kuijk C, Nevitt M. "Vertebral fracture assessment using a semiquantitative technique." *Journal of Bone & Mineral Research* 1993; Vol. 8, No. 9; pp 1137-1148.

[2] Hanley JA, McNeil BJ. "The meaning and use of the area under a receiver operating characteristic (ROC) curve." *Radiology* 1982; Vol. 143; pp 29-36.

[3] CC Glüer et al. *Osteoporosis Int* 1995; Vol. 5: pp 262-270.