Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Dr. Ewa Czerska at (301) 594-1212 x119.

Sincerely yours,

Nancy C Brogdon

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It

allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1)Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a)unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b)reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each

identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1)A mix-up of the device or its labeling with another article.

(2)Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a)has not been addressed by the device's labeling or

(b)has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3)Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of

information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1)May have caused or contributed to a death or serious injury; or

(2)Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1. GENERAL INFORMATION

Generic Name:	Ultrasound Bone Sonometer
Device / Trade Name:	UBIS 5000
Applicants name and address:	Diagnostic Medical Systems Parc De La Mediterranee District De Montpellier 34470 Perols, France
Applicant's U.S. Representative:	Frank Ferguson Ferguson Medical P.O. Box 12038 La Jolla, CA 92039-2038
PMA number:	P000055
Date of Good Manufacturing Practice Inspection:	October 2-5, 2000
Date of notice of approval to the Applicant:	July 17, 2001

2. INDICATIONS FOR USE

The UBIS 5000 is a quantitative ultrasound (QUS) bone sonometer to be used for the measurement of broadband ultrasound attenuation (BUA) of the calcaneus, as an aid to diagnose osteoporosis and to estimate the risk of subsequent atraumatic fracture. The output is expressed in terms of both BUA and T-score.

3. CONTRAINDICATIONS

None.

4. WARNINGS

a) Do not use on a foot that has ever had a heel fracture.
b) Do not use on a foot with edema (excess water/swelling).
c) Do not use on a foot with any skin abrasion.
d) Do not use on patients with leg paralysis.
e) Do not use on patients with a lower extremity prosthesis.

f) Do not use on patients under the age of 20 years old, as there is no reference database available for this age group.
g) Patients must not move their foot during the scanning operation. Such movement can cause inaccuracies in both the image and the BUA measurement.
h) Change the water and process the footwell between patients following the cleaning and disinfection instructions.

5. PRECAUTIONS

a) Users should read the Operators Manual before prescribing UBIS 5000, or interpreting the results. UBIS 5000 should always be switched ON/OFF using the Main Switch located at the rear of the Scanner. Do NOT individually switch off the PC, the Monitor, or the Printer.
b) Only use the UBIS 5000 indoors, in a clean dry environment. Failure to do so could result in unsatisfactory results.
c) Do not store the UBIS 5000 near either a heat source or air conditioner.
d) The UBIS 5000 should not be moved while there is water in the footwell, as this may cause spillage into the interior of the machine.
e) Use only DMS-approved Ultrasound Solution.
   - This product is irritating to the eyes and skin when it is undiluted. In case of direct contact with either the eyes or skin, immediately wash off with water and ask your physician for special advice.
   - Always rinse your hands immediately after use.
   - In case of ingestion, do not make the person vomit and immediately call for a physician and show the cover or label of the product.
   - Do not use in combination with other products. Toxic gas (chlorine) might be released.
f) Do not use this equipment in the presence of a flammable anaesthetic, oxygen, or nitrous oxide.
g) The UBIS 5000 must not be cleaned with abrasive materials, as this will cause damage to the ultrasound probes.
h) All interfacing equipment (monitor, printer) must meet with IEC 60601-1 or equivalent electrical standards.
i) Do not use portable cellular equipment (walkie-talkies, radio phones, portable telephones) in the proximity of the UBIS 5000 during its operation, as this may impact the accuracy of the measurements.
j) In order to avoid electrical shocks, do not remove the cover from the UBIS 5000. The UBIS 5000 contains no user-serviceable parts.

6. DEVICE DESCRIPTION

UBIS 5000 (Ultrasound Bone Scanner) is a quantitative ultrasound (QUS) bone sonometer which measures bone properties at the calcaneus using non-audible high-frequency sound waves. The device consists of a dedicated PC, water-bath scanner, and accessories.

The UBIS 5000 measurements are made with the patient seated in a chair with her/his foot placed in the footwell. The heel is surrounded by approximately 0.35 liters of water (replaced after each scan) heated to approximately 30°C (86°F). The water is an optimum medium for the transmission of ultrasound. A focused transducer on one side of the heel converts an electrical signal into a sound wave which passes through the water and the patient's heel. A second focused transducer on the opposite side of the patients heel receives the sound wave and converts it into an electrical signal that is analyzed by the UBIS 5000 software. This is repeated a total of 3600 times to provide a scanning area of 60mm x 60mm. UBIS 5000 software thus creates an image scan of the complete calcaneus, from which a specific region of interest (ROI) (a 14 mm diameter circle) is automatically selected, based on the area of lowest attenuation. This allows UBIS to adapt the region of interest to the anatomy of each patient, and avoids inconsistent readings that are possible with a system using fixed transducers.

The results are given as Broadband Ultrasound Attenuation (BUA) – in dB/MHz. This ultrasound parameter is based on the frequency dependent attenuation, with the higher BUA values corresponding to lower risk of fracture, and vice versa. BUA is defined as the slope of frequency dependent attenuation between 200 and 600 kHz. It is therefore an attenuation divided by a frequency, measured in dB/MHz. The assessment of BUA is based on the comparison between an ultrasonic wave transmitted through the bone and another wave transmitted in water. These two measurements allow one to calculate the attenuation as a function of frequency, the BUA. BUA gives a good assessment of fracture risk.

Before the BUA measurement can be used for a diagnosis it needs to be compared to the average value of young normal Caucasian females. This comparison is done using an index called T-score, which represents the BUA value on a normalized scale. T-score below (above) zero corresponds to a bone weaker (stronger) than that of the average young normal Caucasian woman. The T-score is the recommended parameter for assessing the risk of fracture.

Comparing the actual BUA value to the average value in a healthy population of the same gender, ethnic origin, and age, when expressed in terms of standard deviations (SDs) of that population, is called Z-score, which can be used as an aid in the detection of conditions associated with non-age-related bone loss.

The UBIS 5000 is controlled directly by the dedicated computer. All instructions and examination results are maintained in the computer, along with a software version of the User Manual. UBIS 5000 allows the possibility to back-up the results onto disk. Hardcopy printouts of the examination results are possible using an external printer.

A UBIS examination includes the following steps: stabilization test, calibration, scan, and a signal and image processing operation.

The stabilization test ensures that the conditions of measurement are correct. This test is based on repeated scans of the heel. Each pre-scan lasts 1 minute and produces a low resolution image. This image allows the software to calculate the coordinates of an ROI.

From the assessment of ultrasound parameters in this ROI, the software will automatically determine if the measurement conditions are correct.

Once these requirements are met, the calibration stage will start automatically. This measurement is carried out in the water, using a dedicated path found under the foot. It will be used as a reference measurement to calculate BUA and SOS. This same measurement is also used for an automatic test of the system, generating an error message if the signal does not have the expected properties.

Having satisfied the calibration stage, the system proceeds with the main scan of the foot, lasting 2 minutes.

The software will thus re-build the ultrasound image, which can be considered as a map of BUA. It then calculates the ROI, defined as the region of minimum attenuation in the postero-inferior part of the calcaneus.

UBIS 5000 then makes the calculation of the mean BUA found in the ROI. This combination of a digital image of the foot and an automatic ROI detection algorithm is the key to UBIS 5000. It enables the measurement of bone properties at a reproducible location of the heel, taking into account each time the patient's anatomy and its position relative to the ultrasound transducers. This technology increases the precision of the measurement, as well as its diagnostic value, i.e., its ability to detect patients at risk of fracture.

7. ALTERNATIVE PRACTICES & PROCEDURES

Alternative methods for assessing bone status include single energy x-ray absorptiometry (SXA), dual energy x-ray absorptiometry (DXA), quantitative computed tomography (QCT), single photon absorptiometry (SPA), and dual photon absorptiometry (DPS). Of these techniques, SXA, DXA and SPA have been used specifically for the estimation of bone mineral density (BMD) of the calcaneus. These established techniques estimate BMD at a variety of anatomical sites, including the heel, by measuring the attenuation of x-rays due to passage through the bone. In addition, there are several bone sonometers that are currently being marketed for assessment of a patient's skeletal status (fracture risk).

8. MARKETING HISTORY

UBIS has been commercially available in markets outside the United States since 1996. The model UBIS 5000, available since 1998, has sold in excess of 720 units in 28 countries world-wide, in Europe, Latin America, Asia and the Middle East. No UBIS 3000 or UBIS 5000 has ever been withdrawn from any market due to reasons related to safety or effectiveness.

9. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

None known.

10. PRE-CLINICAL STUDIES

a) Electrical Safety

Diagnostic Medical Systems (DMS) certified compliance of the UBIS 5000 with the general safety requirements of IEC 60601-1:1996 and the electrical safety requirements of IEC 60601-1-1:1996.

b) Electromagnetic Compatibility

DMS certified compliance of the UBIS 5000 with the electromagnetic compatibility requirements of IEC 60601-1-2:1996 (EMC Directive 89/336/CEE).

c) Ultrasound Acoustic Evaluation

Three ultrasound transmitting/receiving probes were tested in accordance with Track 1 of the Food and Drug Administration (FDA) 510(k) guidance document entitled "Measuring and Reporting Acoustic Output of Diagnostic Ultrasound Medical Devices," (1985). The acoustic output values were within the 510(k) limits specified in FDA's guidance "Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers" (1997).

	Probe 1	Probe 2	Probe 3	Typical Uncertainty
	0.24	0.27	0.20	20%
	0.16	0.18	0.14	13%
	190	170	100	26%
	240	210	131	25%
	0.72	0.73	0.77	7%

Table 1- *Acoustic Ouput Values*

d) Software

The UBIS 5000 software was classified as minor level of concern. Software hazard risk analyses were carried out and showed that all hardware, software, and user concerns were adequately addressed. Verification, validation, and unit testing demonstrated that the device operated in a manner as described in the specifications.

e) Biological / Sterility

The patient contact materials used in the UBIS 5000 are ones which have been used in the medical field without any known adverse effects or reactions. No testing was done, since the safety of the contact materials was well established.

The units are to be cleaned with a disinfectant between patients. The labeling provides specific instructions on how to ensure the effective use of the disinfectant.

The Ultrasound Solution contains chemicals known in the medical field and provides no risk to the patient at the concentrations employed. No testing was deemed necessary.

11. SUMMARY OF CLINICAL STUDIES

Clinical studies were conducted to assess the safety and effectiveness of the UBIS 5000, a quantitative ultrasound bone sonometer device, as an aid to establish the diagnosis of osteoporosis and to identify patients with high risk of osteoporotic fracture. These clinical studies were aimed at meeting the following objectives:

- To establish a U.S. Reference Database for the BUA (in dB/MHz) of UBIS 5000 on healthy or non-fractured Caucasian U.S. women aged 20 to 79 ("Reference Database Study").

- To estimate the in-vivo short-term precision of the BUA obtained by UBIS 5000 ("Precision Study").

- To establish the capacity of UBIS 5000 BUA a) to assess the risk of fracture, b) to discriminate between patients who have suffered atraumatic fractures and age-matched control subjects who have never had an atraumatic fracture, and c) to compare the performance of the device with those of one DEXA and two QUS systems, in order to assess possible bias in selection of control patients ("Fracture Risk Studies").

Clinical studies were carried out in two U.S. centers, located in Massachusetts and California, and in one European center, located in Switzerland. The same protocol was followed in all the centers.

a) Reference Database Study

Four hundred seven (407) healthy Caucasian U.S. females, ranging in age from 20 to 79 years, were used to establish the normality curve. A segmental linear regression analysis based on a moving average over ten years of range with a step of five years gave the following result for the normality curve:

From 20 to 50 years old, $BUA = 0.0066Age_j + 64.573$
From 51 to 59 years old, $BUA = -0.3088Age_j + 80.538$
From 60 to 79 years old, $BUA = -0.0746Age_j + 66.585$

The normality curve of UBIS 5000 BUA for Caucasian U.S. women is displayed in the Figure 1, showing that between 50 and 59 years old (post menopause) the BUA significantly declines by 2.8 dB/MHz (i.e., around 65% of the range). Then, between 60

and 79 years old, the BUA declines by an average of 0.75 dB/MHz per decade (i.e., around 17% of the range).

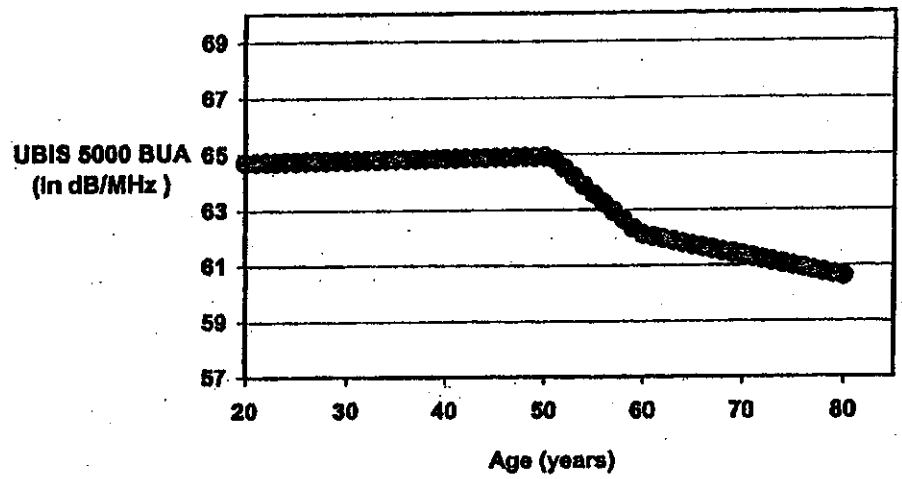

Figure 1 - *Normality Curve of UBIS 5000 BUA for Caucasian U.S. Women*

The 20-39 age range was selected for the representative sample of the young normal Caucasian U.S. female reference population. This young reference population's mean BUA, as well as its standard deviation (SD), were calculated for the purpose of generating T-scores. (See Table 2.)

	Value	95% Confidence Interval
Mean BUA UBIS 5000	64.8	64.2 – 65.4
Standard Deviation	4.1	3.3 - 4.8

Table 2- *Young Reference Value for UBIS 5000 BUA (Data From 171 U.S. Caucasian Females, Ages 20 to 39)*

Given the previous results, the T-score of the patient "j" is calculated as follows:

$$T-score_j = \frac{BUA_j - 64.8}{4.1}$$ where BUA_j is the BUA measured on the patient "j".

In order to calculate the Z-score, the SD of the BUA for the 50-79 age group was calculated: $SD_{50\text{-}79} = 5.0$ dB/MHz. The Z-score of patient "j" is calculated as follows:

From 40 to 50 years old, $$Z-score_j = \frac{BUA_j - 0.0066\,Age_j - 64.573}{5.0}$$

From 51 to 59 years old, $Z-score_j = \frac{BUA_j + 0.3088\,Age_j - 80.538}{5.0}$

From 60 to 79 years old, $Z-score_j = \frac{BUA_j + 0.0746\,Age_j - 66.585}{5.0}$

where Age_j is the age of the patient "j".

b) Precision Study

Fifty-eight (58) subjects ranging in age from 20 to 79 were recruited by the two U.S. centers and used to assess the measurement reproducibility. Each subject was examined three times with UBIS 5000, with foot repositioning before each examination.

Precision was evaluated by calculating the RMS SD, the RMS CV, the CV , the SCV, $longPE_{cc}$, and the TSD. (Refer to attached labeling for definitions.) Results are displayed in Table 3.

	BUA UBIS 5000
RMS SD	0.41 dB/MHz
RMS CV	0.65 %
CV	0.50 %
SCV	2.18 %
$LongPE_{cc}$	3.1 years
TSD	0.10

Table 3- *Results of the Evaluation of the UBIS 5000 Precision (58 U.S. Subjects Aged between 20 to 79)*

c) Correlation Study

Fifty-four subjects ranging in age from 20 to 79 enrolled by the Californian center. Each subject had an examination on the same foot with UBIS 5000 as well as with a LUNAR PIXI according to the Operator's Manual.

Results showed that UBIS 5000 BUA and heel BMD obtained with LUNAR PIXI were correlated with a correlation coefficient of Pearson of r=0.89. This demonstrates a lack of significant bias in the selection of the control patients.

d) Fracture Risk Studies

Two fracture risk studies were independently carried out in the Swiss and California centers.

Tables 4 and 5 show that the UBIS 5000 measurements for the fractured subjects, when expressed in T-score or in Z-score, are similar to neck or spine BMD, or to QUI and stiffness results.

	Controls	Fractured	Z-score	T-Score
BUA UBIS 5000	61.5 ± 5.0	57.2 ± 4.8	-0.8	-1.9
Neck BMD	0.694 ± 0.111	0.614 ± 0.111	-0.6	-1.5
Spine BMD	0.954 ± 0.141	0.839 ± 0.141	-0.7	-2.1

Table 4- *California Center, UBIS 5000 and DEXA Parameters of the Two Groups Expressed in Z-score and T-score*

	Controls	Fractured	Z-score	T-Score
BUA UBIS 5000	60.4 ± 5.1	54.6 ± 4.9	-1.1	-2.5
QUI (Hologic)	75.9 ± 16.1	57.4 ± 17.8	-1.2	-2.4
Stiffness (Lunar)	72.7 ± 12.7	57.1 ± 12.2	-1.2	-2.6

Table 5- *Swiss Center, UBIS 5000 and QUS Parameters for the Two Groups Expressed in Z-score and in T-score*

For each center, non-adjusted and adjusted Odds Ratios per standard deviation decrease were estimated, with their 95% confidence intervals, and the areas under the ROC curves were obtained (see Tables 6and 7).

	Non-Adjusted Odds Ratios (95% CI)	Adjusted Odds Ratios* (95% CI)	Area under the ROC Curve** (95% CI)
BUA UBIS 5000	2.55 (1.55 - 4.20)	1.84 (1.15 - 3.37)	0.73 (0.62 - 0.81)
Neck BMD	2.25 (1.36 - 3.72)	1.69 (1.05 - 3.01)	0.71 (0.61 - 0.81)
Spine BMD	2.40 (1.48 - 3.87)	2.23 (1.37 - 3.86)	0.74 (0.63 - 0.82)

*Adjusted by age, weight, and height.
**Not adjusted by age.

Table 6- California center, Odds Ratios per Standard Deviation Decrease and Area under the ROC Curve for each Bone Parameter

	Non-Adjusted Odds Ratios (95% CI)		Adjusted Odds Ratios* (95% CI)		Area under the ROC Curve** (95% CI)	
BUA UBIS 5000	3.74	(2.12 - 6.60)	3.15	(1.57 - 6.31)	0.81	(0.72 - 0.88)
QUI (Hologic)	3.92	(2.11 - 7.26)	2.89	(1.39 - 5.98)	0.82	(0.73 - 0.89)
Stiffness (Lunar)	4.62	(2.43 - 8.79)	3.70	(1.77 - 7.71)	0.82	(0.73 - 0.89)

*Adjusted by age, weight, and BMI.
**Not adjusted by age.

Table 7- Swiss Center, Odds Ratios per Standard Deviation Decrease and Area under the ROC Curve for each Bone Parameters

ROC curves as well as Odds Ratios analysis showed no statistical difference between UBIS 5000 and DEXA technique or QUS systems (thus demonstrating the absence of any significant bias in selection of control patients), and also demonstrating the ability of the UBIS 5000 to discriminate between fractured subjects and controls.

12. CONCLUSIONS DRAWN FROM THE STUDIES

a) Risk/Benefit Analysis

The UBIS 5000 is a useful clinical indicator of skeletal status, the clinical effectiveness of which is comparable to that of established densitometry (BMD), but without the exposure to ionizing radiation. The power level of ultrasound is significantly lower than the accepted safe levels. It is reasonable to conclude that the benefits of an ultrasound bone imaging system of UBIS 5000 outweigh the risk of illness or injury when used in accordance with the directions for use.

b) Safety

The safety of UBIS 5000 has been demonstrated during the clinical evaluation, with no reports of adverse events or side effects. This clinical experience is consistent with the worldwide experience with UBIS 5000.

c) Effectiveness

The results of the clinical studies demonstrate that both the capacity of UBIS 5000 BUA to discriminate between osteoporotic and non-osteoporotic subjects, and its ability to assess risk of fracture are comparable with those of the spine and hip BMD obtained by DXA absorptiometry technique, as well as those of the ultrasound parameters obtained by two other FDA-approved QUS systems. BUA measured by UBIS 5000 has good precision. Therefore, UBIS 5000 can be used as an aid to diagnosing osteoporosis and to estimate the risk of subsequent atraumatic fracture.

13. PANEL RECOMMENDATION

In accordance with the provisions of section 515 (c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Radiology Devices Panel, a FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

14. FDA DECISION

The applicant's manufacturing facility was inspected on October 2-5, 2000, and was found to be in compliance with the Quality Systems regulations. FDA issued an approval order on July 17, 2001.

15. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

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.

Hazards to Health From Use of the Device: See Indications, Contraindications, Warnings, and Precautions in the attached labeling.

a) Glen M Blake, Heinz W Wahner and I Fogelman, The evaluation of osteoporosis: DEXA and ultrasound in clinical pratice, 1999, 16: 361-363

b) Gluer CC, Blake G, Lu Y, Blunt BA, Jergas M, Genant HK. Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. Osteoporos Int 1995;5(4):262-70.

c) CG Miller, RJ Herd, T Ramalingam, I Fogelman, GM Blake Ultrasonic Velocity Measurement Through the Calcaneus: which velocity should be measured, Osteoporosis Int , 1993.

d) Claus-C. Glüer, How to characterize the ability of diagnostic technique to monitor the skeletal changes. Journal of Bone and Mineral Research 1997; 12: S378.

Essential Prescribing Information

Introduction and Background Information

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

1.1. Description of the device

UBIS 5000 (Ultrasound Bone Scanner) is a quantitative ultrasound (QUS) bone sonometer which measures bone properties at the calcaneus using non-audible high-frequency sound waves. The device consists of a dedicated PC, water-bath scanner, and accessories.

The UBIS 5000 measurements are made with the patient seated in a chair without wheels, in front of the device with her/his foot placed in thefootwell. The heel is surrounded by approximately 0.35 liters of water (replaced after each scan) heated to approximately 30°C (86°F). The water is an optimum medium for the transmission of ultrasound. A focused transducer on one side of the heel converts an electrical signal into a sound wave which passes through the water and the patient's heel. A second focused transducer on the opposite side of the patients heel receives the sound wave and converts it into an electrical signal that is analyzed by the UBIS 5000 software. This is repeated a total of 3600 times to provide a scanning area of 60mm x 60mm. UBIS 5000 software thus creates an image scan of the complete calcaneus, from which a specific ROI (a 14 mm diameter circle) is automatically selected, based on the area of lowest attenuation. This allows UBIS to adapt the region of interest to the anatomy of each patient, and avoids inconsistent readings that are possible with a system using fixed transducers.

The results are given as broadband ultrasound attenuation (BUA, in dB/MHz). This ultrasound parameter is based on the frequency dependent attenuation, with the higher BUA values corresponding to lower risk of fracture, and vice versa.

Before the BUA measurement can be used for a diagnosis it needs to be compared to the average value of the young normal Caucasian females. This comparison is done using an index called T-score, which represents the BUA value on a normalized scale. T-score above (below) 0 corresponds to a bone stronger (weaker) than that of the average young normal Caucasian women. The T-score is the recommended parameter for assessing the risk of fracture.

Comparing the actual BUA value to the average value in a healthy population of the same gender, ethnic origin, and age, when expressed in terms of standard deviations (SDs) of that population, is called Z-score, which can be used as an aid in the detection of conditions associated with non-age-related bone loss.

1.2. Indications For Use

The UBIS 5000 is a quantitative ultrasound (QUS) bone sonometer to be used for the measurement of broadband ultrasound attenuation (BUA) of the calcaneus, as an aid to diagnose osteoporosis and to estimate the risk of subsequent atraumatic fracture. The output is expressed in terms of both BUA and T-score.

1.3. Contraindications

None.

1.4. Warnings

1. Do not use on a foot that has ever had a heel fracture.
2. Do not use on a foot with edema (excess water/swelling).
3. Do not use on a foot with any skin abrasion.
4. Do not use on patients with leg paralysis.
5. Do not use on patients with a lower extremity prosthesis.
6. Do not use on patients under the age of 20, as there is no reference database available for this age group.
7. Patients must not move their foot during the scanning operation. Such movement can cause inaccuracies in both the image and the BUA measurement.
8. Change the water and process the footwell between patients following the cleaning and disinfection instructions.

1.5. Precautions

1. Users should read the Operators Manual before prescribing UBIS 5000, or interpreting the results.UBIS 5000 should always be switched ON/OFF using the Main Switch located at the rear of the Scanner. Do NOT switch off individually the PC, the Monitor, or the Printer.
2. Use the UBIS 5000 only indoors, in a clean dry environment. Failure to do so could result in unsatisfactory results.
3. Do not store the UBIS 5000 near either a heat source or air conditioner.
4. The UBIS 5000 should not be moved while there is water in the footwell, as this may cause spillage into the interior of the machine.
5. Use only DMS-approved Ultrasound Solution.
   - This product is irritating to the eyes and skin <u>when it is undiluted</u>. In case of direct contact with either the eyes or skin, immediately wash off with water and ask your physician for special advice.
   - Always rinse your hands immediately after use.
   - In case of ingestion, <u>do not make the person vomit</u> and immediately call for a physician and show the cover or label of the product.
   - Do not use in combination with other products. Toxic gas (chlorine) might be released.

6. Do not use this equipment in the presence of a flammable anesthetic, oxygen, or nitrous oxide.
7. The UBIS 5000 must not be cleaned with abrasive materials, as this will cause damage to the ultrasound probes.
8. All interfacing equipment (monitor, printer) must meet with IEC 60601-1 or equivalent electrical standards.
9. Do not use portable cellular equipment (walkie-talkies, radio phones, portable telephones) in the proximity of the UBIS 5000 during its operation, as this may impact the accuracy of the measurements.
10. In order to avoid electrical shocks, do not remove the cover from the UBIS 5000. The UBIS 5000 contains no user-serviceable parts.

1.6. Adverse Events

None known.

1.7. Maintaining Device Effectiveness

The physician/operator should routinely clean the UBIS 5000 with non-abrasive materials. The Quality Control test is automatically carried out before each examination on an internal phantom. Graphic and statistic display of the results can be accessed from the main menu. The physician/operator does not have access to the internal parts of the device.

1.8. Patient Counseling Information

Supplied with the UBIS 5000 are patient brochures titled "Information for Patients." These documents can be freely re-duplicated or can be ordered from DMS.

Further information on osteoporosis can be obtained from *National Osteoporosis Foundation, 1150 17th Street, N. W. Suite 500, Washington , D. C. 20036-4603, Tel : (202) 223-2226.*

1.9. How the UBIS 5000 is supplied

The UBIS 5000 is supplied as a complete operational unit, with a dedicated computer and all the accessories required to operate it. The monitor and the printer may be supplied by either the customer or by DMS.

2. Clinical Studies

Clinical studies were conducted to assess the safety and effectiveness of the UBIS 5000, a quantitative ultrasound bone sonometer device, as an aid to establish the diagnosis of osteoporosis and to identify patients with high risk of osteoporotic fracture. These clinical studies were aimed at meeting the following objectives: