DE NOVO CLASSIFICATION REQUEST FOR SONABLATE® 450

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **High intensity ultrasound system for prostate tissue ablation**. A high intensity ultrasound system for prostate tissue ablation is a prescription device that transmits high intensity therapeutic ultrasound (HITU) energy into the prostate to thermally ablate a defined, targeted volume of tissue, performed under imaging guidance. This classification does not include devices that are intended for the treatment of any specific prostate disease and does not include devices that are intended to ablate non-prostatic tissues/organs.

NEW REGULATION NUMBER: 21 CFR 876.4340

CLASSIFICATION: II

PRODUCT CODE: PLP

BACKGROUND

DEVICE NAME: SONABLATE® 450

SUBMISSION NUMBER: DEN150011

DATE OF DE NOVO: MARCH 24, 2015

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REQUESTER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

The Sonablate® 450 is indicated for transrectal high intensity focused ultrasound (HIFU) ablation of prostatic tissue.

LIMITATIONS

The sale, distribution, and use of the Sonablate® 450 is limited to prescription use only.

Use of the Sonablate® 450 must be prescribed and administered under the direct supervision of a qualified and trained physician, after appropriate urologic patient evaluation.

Limitations on device use are also achieved through the following statements included in the Instructions for Use:

Contraindications:

- Large (> 10 mm) cysts or calcifications in the planned ablation zone
- Metal implants or stents in the urethra
- Brachytherapy seeds in the planned ablation zone
- Pre-existing inflammatory disease of the colon or rectum (such as proctitis or ulcerative colitis)
- Prior significant rectal surgery
- Inability to insert or tolerate a transrectal ultrasound probe
- Active urinary tract infection
- Urethral stricture
- Latex allergy

Warnings:

The effectiveness of the Sonablate® 450 in treating any specific prostate disease has not been established.

The safety and effectiveness of the Sonablate® 450 have not been established in patients with the following conditions:

- interest in future fertility,
- bleeding disorders,
- clinical or histological evidence of urinary bladder cancer,
- renal impairment,
- functional bladder problems, including neurological disorders that might affect bladder function,
- post-void residual urine > 250 mL,
- urinary retention requiring an indwelling catheter,
- enlarged medial lobe of the prostate protruding into the urinary bladder,
- clinical evidence of prostatitis within 6 months prior to HIFU,
- bladder calculus, and
- prostates > 40 cm^3.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Sonablate® 450 is a computer-controlled device designed for transrectal delivery of high intensity focused ultrasound (HIFU) energy to the prostate to ablate regions of unwanted prostatic tissue via thermal ablation. The device makes use of integrated biplanar ultrasound imaging for real-time monitoring, planning, and pre- and post-ablation imaging of the prostate. The system consists of the following main components:

Sonasource Console:

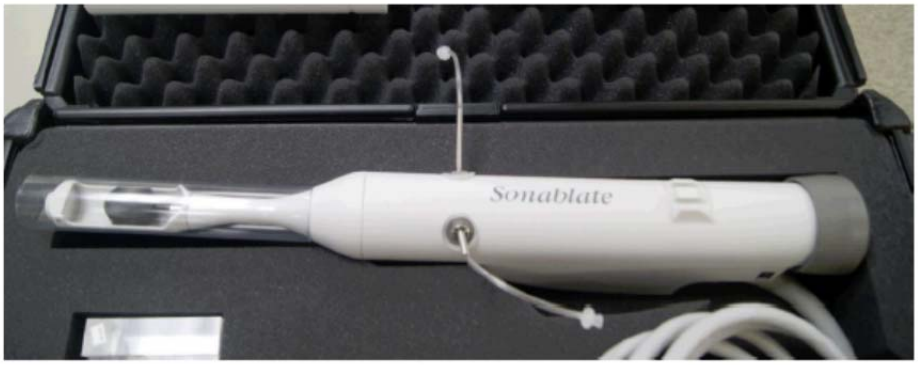
The Sonasource Console contains the system computer and electronics for HIFU planning and delivery. The monitor displays all system, patient, imaging, and HIFU delivery information via a graphical user interface. The keyboard and trackball are used for data and user-command entry. The trackball allows the operator to define the dimensions of the target zone and to measure the tissue distance from the rectal wall to the center of the target zone.

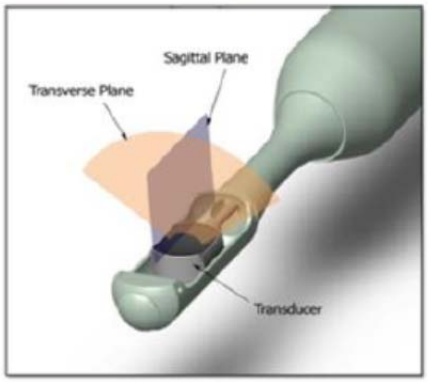
Planning is performed under physician control, while HIFU delivery is automatically performed by the system under physician monitoring.

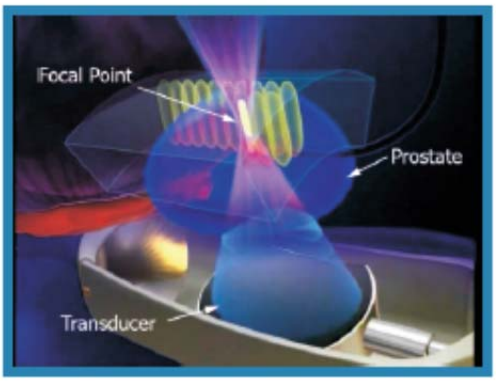
Key system features:

- Rectal Wall Distance (RWD) monitor: A feature used by the system to continually measure the distance between the therapy transducer and the rectal wall, to maintain a safe distance.
- Reflectivity Index Monitor (RIM): A feature used by the system to detect undesired/excessive cavitation bubble formation at the rectal wall.
- Dual Stack: A visual aid tool for the physician to use during planning, which allows rapid view of sequential transverse and linear images.
- MR/US Fusion: Fuses the ultrasound image with a prior magnetic resonance (MR) image.

Sonablate Probe 30/40:







The Sonablate Probe 30/40 (probe) is designed to provide gray-scale ultrasound images of the prostate and to deliver HIFU pulses to targeted tissue while minimizing damage to intervening tissue. Prior to HIFU application, the probe is inserted into the patient's rectum, with the ultrasound transducers positioned at the level of the prostate. The probe has a dual-sided piezoelectric transducer, with different curvatures (i.e., 30 mm and 40 mm focal lengths) on opposite sides. The dual-sided transducer allows focal HIFU application of the entire volume of prostate tissue using only one transrectal probe (30 mm transducer for the posterior region of the gland, 40 mm probe for the anterior region).

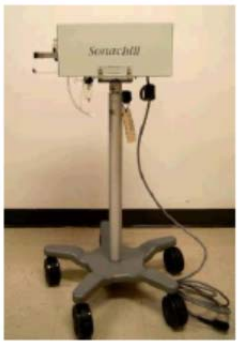
The probe is connected to the Sonasource Console via a cable. Prior to insertion in the patient, the tip of the probe is covered with a single use probe sheath (an off the shelf condom), which is secured by O-rings.

The probe incorporates two motors (linear and sector) to guide transducer movement, dedicated, closed loop coolant water path, and a thermistor for temperature control. To reduce the possibility of thermal injury to the rectal wall, HIFU application is automatically terminated if the probe temperature exceeds 30°C.
In the Imaging Mode, the transducer moves in a longitudinal direction to provide linear images of the prostate and oscillates in the transverse plane for sector images. In the Therapy Mode, the transducer sequentially moves to pre-specified positions (determined during HIFU planning), and stays at each position while the energy is delivered to the tissue. Each thermal lesion created in the prostate is 10-12 mm in length and 1-2 mm wide. Multiple lesions must be sequentially positioned within the prostate to fill the intended tissue volume.

Key technical specifications:

- Two piezoelectric crystals of different curvatures – 30 mm and 40 mm focal lengths on opposite sides
- Focal lengths: 30 mm +2.0/-1.0 mm, 40 mm +2.0/-1.0 mm
- Site intensity in the focal zone 1200 to 2000 W/cm^2
- Pulse ON/OFF durations: 3 s ON/6s OFF
- HIFU application mode frequency 4.0 MHz
- Imaging mode frequency 6.5 MHz

Sonachill:



The Sonachill circulates degassed cold water to the probe tip (flow contained within the probe sheath). The circulating water functions to cool the rectal wall and HIFU transducer surface, and to provide ultrasound coupling between the transducer and tissue. To prevent contaminated coolant water from the patient entering and contaminating the internal fluid pathways of the Sonachill device (which could occur if the probe sheath breaks), there are two independent fluid pathways. The first fluid path is through the probe and the single use components of the Water Path Kit. The second fluid path is isolated from the probe (i.e., within the Sonachill), and circulates between the heat exchanger and the pump.

Sonablate Multi-Axis Stepper and Probe Arm:

After the probe is inserted in the patient's rectum, the Multi-Axis Stepper and Probe Arm are locked to hold the probe in a fixed position for the duration of the procedure. Adjustments are made to the stepper to optimize the position of the probe in relationship to the probe arm.

Single Use Components:

Single use, disposable components used during a Sonablate® 450 HIFU application are provided in (i) a Probe Tip Kit, and (ii) a Water Path Kit. The Probe Tip Kit contains the single use components to cover and prepare the probe tip for insertion (i.e., probe sheaths (legally marketed condoms), packets of ultrasound transmission gel, O-rings, and O-ring applicator). The Water Path Kit contains the tubing, reservoir, syringe, and other disposable components used to set up and establish coolant water flow between the probe and the Sonachill.

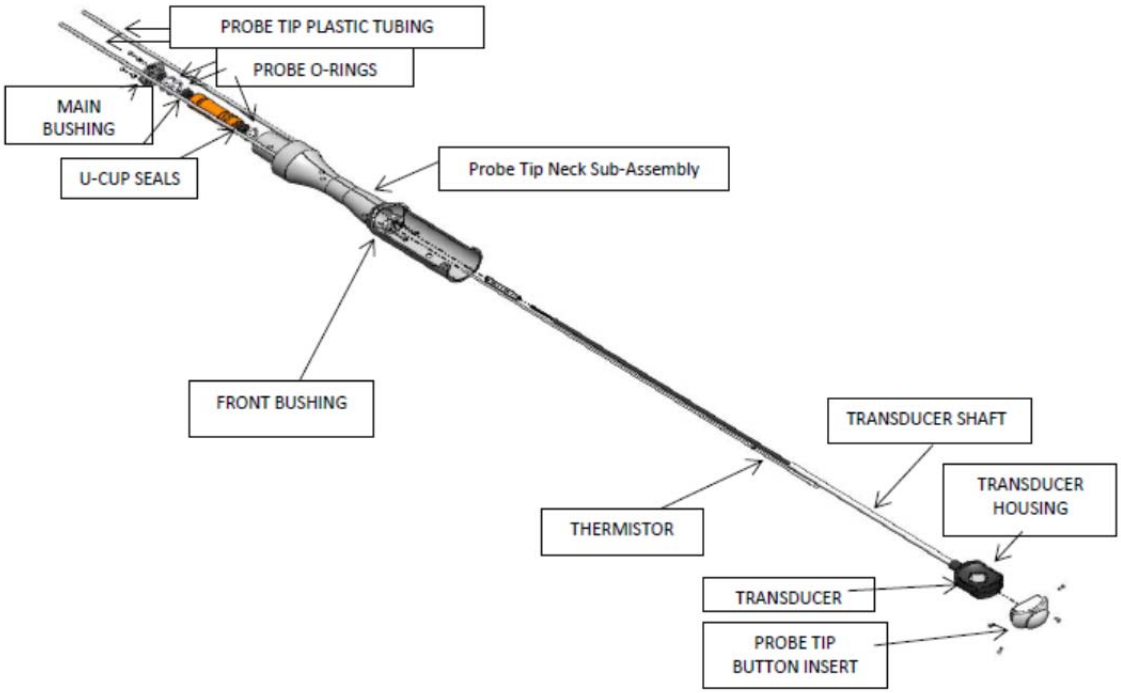
SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

HIFU application time ranges from 2 to 4 hours, and all patient contact is limited to the rectum. Therefore, components that contact the patient have limited (< 24 hr.) contact with intact mucosa. In accordance with ISO 10993-1: Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing within a Risk Management Process, the following biocompatibility tests should be considered given this type and duration of contact: cytotoxicity, sensitization, and intracutaneous reactivity (or irritation).

During normal clinical use, the components/materials that contact the patient are:

Component	Material(s)	Direct/indirect contact	Additional information
Probe sheath	Polyurethane or latex	direct	Off-the-shelf finished device (Regulated under 884.5300)
Ultrasound transmission gel	Water-based, off-the shelf gel	direct	Off-the-shelf finished device Regulated under 892.1570)
O-ring	b(4) ubber	direct	--
Probe components	Various (see diagram and table below)	Direct and indirect (if the probe sheath ruptures)	--
Water Path Kit components	Various (see table below)	indirect (if the probe sheath ruptures)	--


PROBE TIP PLASTIC TUBING
PROBE O-RINGS
MAIN BUSHING
U-CUP SEALS
Probe Tip Neck Sub-Assembly
FRONT BUSHING
TRANSDUCER SHAFT
TRANSDUCER HOUSING
THERMISTOR
TRANSDUCER
PROBE TIP BUTTON INSERT

Components/materials that contact the patient in the event of a probe sheath rupture:

Component	Material(s)	Patient Contact
Collar Material	b(4)	Direct
Probe Tip Neck Material		Direct
Probe Tip Button		Direct
Probe O-rings		Direct
Transducer		Direct
Transducer shaft		Direct
Transducer housing		Direct
U-Cup Seals		Indirect
Thermistor		Indirect
Front Bushing		Indirect
Probe Tip Neck SubAssembly		Indirect
Main Bushing		No contact
Shaft to housing assembly		Direct
Procedure Treatment Kit 1. reservoir assembly 2. 2 Masterflex Tubing 3. Tygon flexible plastic tubing (5x6 inches, 18 inches, 2x24 inches) 4. 2 Syringe assembly 5. 7 male luer lock to barb connectors 6. 10 Female Luers 7. 2 inline Degasser Filters 8. 3 port Y infusion 9. 4 Male Luers with taper 10. tygon double lumen tubing 11. blue luer nylon insert assembly 12. red male luer		Indirect
Reservoir Bottle		Indirect
Lubriseal		Indirect

The probe sheath and ultrasound transmission gel are legally marketed products classified under separate classification regulations, and obtained by SonaCare in final, finished form. Because the probe sheath and ultrasound transmission gel are legally marketed medical devices, no further biocompatibility testing is needed.

The components of the probe tip, Probe Tip Kit, and Water Path Kit that directly or indirectly contact the patient in instances of probe sheath breakage, including the O-rings that are used to secure the probe sheath to the probe tip, separately underwent cytotoxicity, sensitization, acute systemic toxicity, and irritation testing in accordance with ISO 10993 methods, and the results were found to be acceptable.

SHELF LIFE/STERILITY/REUSE

Sterilization:

The Probe Tip Kit and Water Path Kit are packaged by SonaCare Medical in a polyethylene tray with Tyvek lid, and are sterilized by b(4) to ensure a sterility assurance level of 10^{-6}. The sterilization process validation and routine monitoring comply with ISO 11137 (Sterilization of Health Care Products – Requirements for Validation and Routine Control – Radiation Sterilization).

The hardware components andsubassemblies that comprise the Sonablate® 450 (i.e., Sonasource Console, Sonachill, probe, multi-axis stepper, and probe arm) are provided non-sterile for reuse.

Shelf Life:

The components of the Probe Tip Kit have individually-labeled expiration dates (i.e., the probe sheaths and packets of ultrasound transmission gel are legally marketed devices with expiration dates from the original manufacturers, and the O-rings and O-ring applicator are labeled with a 3-year shelf life based on stability testing conducted by SonaCare Medical). Therefore, the labeled shelf life of the Probe Tip Kit is based on the minimum (soonest) expiration date of the internal components. A 3-year shelf life of the sterile packaging of the Probe Tip Kit components is supported by accelerated shelf life testing of packaging integrity (i.e., seal strength and bubble emission tests).

The Water Path Kit is labeled with a 12-month shelf life. This shelf life is supported by accelerated shelf life testing of packaging integrity (i.e., seal strength and bubble emission tests) and component functional integrity/performance.

Reuse:

The hardware components/subassemblies that comprise the Sonablate® 450 (i.e., Sonasource console, Sonachill, probe arm, multi-axis stepper, and probe) are reusable, and must be either cleaned, or cleaned and either high level disinfected or sterilized, between uses:

- Sonasource console: cleaning
- Sonachill: cleaning
- Probe arm: cleaning and steam sterilization
- Multi-axis Stepper: cleaning and steam sterilization

- Probe: cleaning, and either high level disinfection (HLD) or ethylene oxide (EO) sterilization

The Sonasource console and Sonachill have non-critical Spaulding classifications, and require only routine manual cleaning of external surfaces between uses.

The probe arm and multi-axis stepper also have non-critical Spaulding classifications, but have increased risk of contamination by the physician's gloved hand. Therefore, the labeling instructs users to both manually clean and steam sterilize these components between uses.

The probe has a semi-critical Spaulding classification, particularly in the event that the probe sheath breaks. Therefore, the probe must be manually cleaned and either undergo HLD or EO sterilization between uses.

Validation testing was performed for each of these reprocessing steps:

- The cleaning validation of each reusable component was adequately performed, and all samples met the pre-specified acceptance criteria.
- The recommended HLD procedure for the probe was validated to achieve a 6-log reduction of mycobacteria. Cytotoxicity testing performed on probes that underwent HLD followed by simulated clinical usage verified that unsafe levels of disinfectant solution do not remain on the device.
- The recommended steam sterilization cycle for the probe arm and multi-axis stepper was validated for a SAL of 10^{-6}.
- The recommended EO sterilization cycle for the probe was validated for a SAL of 10^{-6}. EO residual levels were verified to be below unsafe levels.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

Electromagnetic Compatibility (EMC):

The Sonablate® 450 was evaluated for conformance to IEC 60601-1-2, and was found to comply with all applicable requirements of this EMC testing standard. Emissions were within acceptable levels, and the device exhibited adequate immunity to electromagnetic disturbances. The user's manual was reviewed from the EMC perspective, and was found to contain comprehensive warnings to the user on recognizing and avoiding common situations that could cause electromagnetic interference (EMI), as well as a summary of the EMC testing per the IEC 60601-1-2 standard.

Electrical Safety:

The Sonablate® 450 was evaluated for conformance to IEC 60601-1 (general requirements) and IEC 60601-2-37 (particular requirements for ultrasonic diagnostic and monitoring equipment). Review of the results concluded that the device complies with all of the electrical safety requirements specified in these standards.

SOFTWARE

The Sonablate® 450 software performs/controls the following functions:

- HIFU application procedure,
- Imaging, monitoring, interface with the display, printer, and keyboard,
- Data storage,
- Motors controlling transducer placement,
- Watchdog timer for safety, and
- Alarms.

This information was provided and reviewed in accordance with the FDA documents "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" and "Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software Use in Medical Devices," and found to be complete. Details of the software review are described below:

- The operating system is Windows XP Professional.
- The Sonablate® 450 uses the following off-the-shelf software: Java, Co-routine for Java, SnagIt, and Embedded board code.
- The following software documentation, specified in the FDA document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," was provided and is adequate:

Version: 6.0		
Level of Concern: Major		
	Yes	**No**
Software description	X	
Device Hazard Analysis	X	
Software Requirements Specifications	X	
Architecture Design Chart	X	
Design Specifications	X	
Traceability Analysis/Matrix	X	
Development	X	
Verification & Validation Testing	X	
Revision level history	X	
Unresolved anomalies	X	

PERFORMANCE TESTING – BENCH

Ultrasound characterization and output performance tests:

Transducer characterization:
Ultrasound transducer characterization and calibration tests were performed on the

Sonablate® 450. Specifically, to demonstrate that the ultrasound output from the transducers is consistent and within expected levels, the technical parameters described in the table below were measured:

Transducer Characterization Test Summary:

Test	Purpose	Acceptance Criteria	Results
Schlieren test (Uses images of the therapy and imaging transducers, along and perpendicular to the direction of a propagating light beam, to measure patterns of refraction produced by local changes in water density.)	To measure the beam profile (width) and alignment (misregistration) of each transducer.	b(4)	All test samples (n=7) met the acceptance criteria.
Electrostatic test (Applies an electrical impulse to the transducer, and analyzes the resulting acoustic wave.)	To determine the focal length of each transducer.	b(4)	All test samples (n=7) met the acceptance criteria. These results support the targeting accuracy and reproducibility of the HIFU output.
Force balance test (Measures the mechanical energy produced by the transducer.)	To measure total acoustic power (TAP) from each transducer, and calculate the focal intensity and acoustic pressure.	b(4) *There are no acceptance criteria for focal intensity and acoustic pressure; they were calculated to permit computer modeling of focal site temperature.	All test samples (n=7) met the acceptance criteria. b(4)

Imaging verification:
The tests summarized in the table below were performed to verify the imaging functionality of the ultrasound transducers:

Imaging Verification Test Summary:

Test	Purpose	Acceptance Criteria	Results
Phantom testing using a standard ATS Labs phantom	To measure the following characteristics of each transducer: Linear & sector resolution Penetration depth Signal-to-noise ratio (SNR)	Both transducers: b(4) b(4)	The test sample (n=1) met the acceptance criteria. The resolution is sufficient for tissue differentiation of the prostate and surrounding anatomy.
Imaging frame rate test	To measure the linear and sector frame rate of each transducer.	b(4)	The test sample (n=1) met the acceptance criteria. The frame rate is sufficient to provide feedback to the physician during probe positioning. b(4)
Image display test	To verify that the system is capable of performing transverse and longitudinal imaging using each probe, and simultaneously displaying them	Using each transducer: the system is performs transverse and longitudinal imaging using each probe, and displays them simultaneously	The test sample (n=1) met the acceptance criteria.

HIFUverification/safety:
The tests summarized in the table below were performed to verify the key aspects of the Sonablate® 450 that relate to its therapeutic ultrasound (i.e., HIFU) output:

Verification Test Summary:

Test	Purpose	Acceptance Criteria	Results
Ex vivo tissue phantom tests (HIFU ablation in chicken breast tissue.)	To confirm the maximum ablationvolume and depth that can be achieved by the system	b(4)	The test sample (n=1) met the acceptance criteria. The system is capable of targeting a

	(based on the requirements for prostate use). To verify the dimensions of the HIFU lesions created by each transducer, and that lesions are positioned to create a contiguous volume.	b(4)	tissue volume of up to 40 cm^3, at a depth of up to 40 mm. The system is capable of creating single and volume lesions in x, y, and z dimensions that meet the acceptance criteria. These results support the targeting accuracy and reproducibility of the HIFU output.
HIFU ON-time/OFF-time Verification Testing (Using an oscilloscope to measure the durations of each period of the HIFU application cycle.)	To confirm the ON/OFF timing of th system's HIFU application cycle.	b(4)	The test sample (n=1) met the acceptance criteria. The system meets ON time and OFF time requirements.

General functional/mechanical/performance tests:

SonaCare Medical conducted a variety of tests to verify the proper operation/performance of the system components. These tests included verification of:

- The ability of Sonablate® 450 subsystems (console, probe, chiller) to communicate/interface with one another per design specifications, including simulated use testing.
- Operation of system alarms and automatic application interruption.
- Total acoustic power display (ability of the TAP meter to display this HIFU application parameter).
- Probe coupling performance.
- User interface control of energy.
- Inability to access remotely (i.e., unable to connect to outside communication networks).
- Sonachill fluid cooling performance (temperature, flow rate).
- Multi-axis stepper movement sensitivity, carrying capacity, reliability, and durability.
- Probe arm carrying capacity, resistance to probe motion (when locked), degree of motion (when unlocked), and clamp attachment.

Each of these tests evaluated the device in an environment simulating clinical use, and confirmed that the device (or device component) successfully met the functional requirement of each test.

PERFORMANCE TESTING – ANIMAL

The following animal testing was performed to demonstrate that the Sonablate® 450 thermally ablates targeted tissue in a controlled manner, without unsafe heating or ablation of adjacent, non-target tissues:

- Study 1 ("Safety and Effectiveness of Tissue Ablation"): A dog prostate model study (n=5), which demonstrated that the Sonablate® 450 effectively destroys prostate tissue without rectal wall injury or ablation outside the planned target zones. This study used the 3 seconds ON/6 seconds OFF HIFU application cycle (i.e., the only HIFU application cycle available on the Sonablate® 450). In this study, thermocouples positioned in the prostate and adjacent to the rectal wall documented that the system is capable of raising target tissue temperature to above 60ºC for 3 seconds without rectal wall temperatures exceeding 43ºC. After HIFU application, histological evaluation of the prostate confirmed the presence of tissue coagulation in the targeted volume.
- Study 2 ("Efficacy Improvement Software Test Report – Localization and Ablation"): A dog prostate model study (n=4), which demonstrated (i) the safety and effectiveness of a 90 degree application angle, and (ii) the ablation effectiveness of an alternate application cycle (that is not available on the Sonablate® 450).
- Study 3 ("Treatment Volume and Accuracy Study Report"): This preliminary dog study confirmed accurate spatial localization of a specific target using ultrasound imaging, verifying that temperatures within the focal zone are sufficient to achieve coagulative necrosis (> 60ºC), and that tissue outside of the focal zone (including the rectal wall) do not reach temperatures capable of coagulative necrosis.
- Study 4 ("Thermocouple Response to Treatment Test"): This preliminary dog study compared the accuracy of the planned HIFU application zones versus actual target tissue volume.
- Study 5 ("Safety of HIFU Energy Application to Adjacent Tissues"): This preliminary dog study was performed to verify that energy delivery to prostatic tissue does not damage adjacent structures, and that the use of the Sonachill cooling system during HIFU cools the rectal wall tissue.

Study 1 (primary study) was performed using the Sonablate® 450, whereas Studies 2, 3, 4, and 5 (supporting studies) were performed using a different device version that has several additional features.

SUMMARY OF CLINICAL INFORMATION

Data to support that the Sonablate® 450 safely and effectively ablates prostatic tissue were obtained from the US Salvage Study. In this study, a population of post-radiation patients

received whole gland ablation using the Sonablate® 450 as a treatment for recurrent prostate cancer. While the oncological outcomes from this study are inconclusive, the results provide reasonable assurance of safety and effectiveness of the device in the context of prostate tissue ablation.

The design of the US Salvage Study is briefly summarized below:

- Study Design: Multi-center, non-randomized, prospective, single arm study involving 20 sites (U.S. and Canada) and 200 subjects. Sixteen sites actively enrolled subjects.
- Patient Population: Men (40-85 years of age) with histologically confirmed, organ-confined, recurrent, non-metastatic prostatic adenocarcinoma. All participants had documented disease relapse two or more years following external beam radiation therapy (EBRT). All participants had a prostate specific antigen (PSA) level ≥ 0.5 ng/mL and ≤ 10 ng/mL, and clinical stage T1c-T2 prior to radiation. Participants were candidates for salvage therapy on the basis of an assessment of general health and inter-current comorbidities.
- Endpoints: *Effectiveness* - PSA nadir of ≤ 0.5 ng/mL within 12 months, and negative prostate biopsy at 12 months. *Safety* - Rate of adverse event occurrence by type and severity.
- HIFU Application: Whole gland ablation of the prostate using the Sonablate® 450. All applications were performed under general or regional anesthesia. Prior to application, patients received a suprapubic catheter.
- Follow-Up Exams: Telephone follow-up occurred on day 2 (to assess for signs of infection and subject's comprehension of suprapubic catheter care). Another follow-up occurred to between 2-4 weeks post ablation to remove the catheter. Follow-up visits were scheduled for 6 weeks, 3, 6, 9, 12, months post-ablation, and annually thereafter until 5 years post-ablation.

The original objective of this study was to evaluate device use as a treatment for recurrent prostate cancer. However, to evaluate the safety and effectiveness of the device for the functional indication of prostate tissue ablation, changes were made to the endpoints and associated analyses. Specifically, "ablation effectiveness" was assessed by analyzing changes in prostate volume, PSA level, and negative biopsy rate, assessed at baseline and 12 months post-ablation. Safety evaluations were conducted using patient completed questionnaires and investigator reported adverse events through 12 months post-ablation.

The clinical dataset is based on an interim analysis of the initial 117 patients enrolled (of which 116 underwent HIFU application). Patients ranged in age from 53 to 83 years (mean = 69.8). These men had a mean pre-ablation PSA of 4.9 ng/mL.

Effectiveness:

The following results demonstrate that the Sonablate® 450 effectively ablates targeted prostatic tissue:

- Among the 73 patients who had prostate volumes determined both pre- and post-ablation, the mean reduction in volume was 11.8 cm^3 (95% confidence limits = 9.7, 14.0). This change represents a mean reduction of 46% from the baseline volume. Of the 44 patients

who did not have volumes calculated post-ablation, there was only a single case of a positive biopsy.

- Eighty-three percent (83%) of the total cohort of 117 patients had a reduction in PSA post-ablation (95% confidence limits = 74.6, 89.0). For this analysis, missing data were treated using the last value carried forward method.
- Sixty-one percent (61%) of the total cohort of 117 patients had a negative post-ablation biopsy (95% confidence limits = 51.2, 69.5). For this analysis, 30 patients who did not have a 12-month biopsy were considered "positive."

Safety:

The following adverse events were observed in this whole gland study of post-radiation patients (n=117 unless otherwise noted):

Adverse Event	Percentage of Subjects
Erectile Dysfunction (n=51 potent at baseline)	71%
Urinary Tract Infection	50%
Urinary Incontinence (leak)	47%
Hematuria	43%
Urinary Retention	43%
Urinary Frequency	35%
Urinary Incontinence (pads)	32%
Urinary Urgency	29%
Urinary Tract Obstruction	20%
Dysuria	18%
Urethral Stricture	15%
Epididymitis/Orchitis	8%
Bladder Neck Contracture	5%
Rectal Fistula	4%
Urinary Fistula	2.6%
Osteomyelitis	2.6%

A total of 27 device/procedure related serious adverse events (SAEs) were reported in 21 subjects. These consisted of urinary retention/obstruction (n=6), hematuria (n=5), rectal/urinary fistula (n=5), UTI/urosepsis (n=5), osteomyelitis (n=3), urinary incontinence (n=1), urethral stricture (n=1), and small intestinal obstruction (n=1). Each of these events resolved.

Two patients died during the course of the study, both for reasons unrelated to HIFU application (i.e., aspiration following esophageal surgery, and motor vehicle accident).

Clinical Results Summary:

The observed changes in prostate volume, PSA level, and negative biopsy rate provide complimentary evidence that the Sonablate® 450 is capable of ablating prostate tissue. The observed 46% reduction in total volume of the prostate demonstrates bulk removal of a large quantity of prostatic tissue when a whole-gland strategy is employed with the Sonablate® 450, and the percentage of patients experiencing a PSA reduction post-ablation (i.e., 83%) demonstrates that the ablation effect was achieved in a large majority of study subjects. The increase in negative biopsy rate associated with HIFU application (i.e., from 0% at baseline to 61% at 12 months post-ablation) provides further evidence from histology that Sonablate® 450 ablates prostate tissue.

With the number of patients treated and the duration of follow-up, the risk profile associated with Sonablate® 450 ablation is well-characterized in the context of this study population. In this study, 99% of patients experienced some type of application-related complication. Serious adverse events (SAEs) occurring in the population included urinary retention/obstruction (5%), hematuria (4%), rectal fistula (4%), urinary tract infection (4%), and osteomyelitis (3%). Non-serious adverse events primarily consisted of erectile dysfunction (71%), UTI (54%), urinary incontinence (47%), urinary retention (43%), hematuria (31%), urinary obstruction (20%), and urethral stricture (15%). The duration of a harmful event was dependent on the indication for prostate ablation and current disease status. Some of the harmful events such as voiding symptoms resolve on their own over weeks to months, and some such as infections resolve with medical therapies. Of the three patients with osteomyelitis, one patient underwent cystectomy and ileal conduit diversion. Some of the patients with urinary incontinence and erectile dysfunction resolve spontaneously over a period of months while a significant percentage have lifelong symptoms requiring medical and surgical intervention. These include placement of an artificial urinary sphincter for treatment of incontinence and medications or devices for treatment of erectile dysfunction. The adverse event profile associated with use of the Sonablate® 450 may be different in patients who receive ablation to less than the entire prostate, or who have not had a prior treatment to their prostate.

While this HIFU application using Sonablate® 450 has documented morbidity, the benefits outweigh the risks in certain populations of men seeking ablation of unwanted prostate tissue.

LABELING

Labeling has been provided that includes instructions for use for the physician, and an appropriate prescription statement as required by 21 CFR 801.109. The labeling includes:

- directions on device set-up and HIFU application planning, delivery, and completion using the Sonablate® 450 device;
- a "Clinical Studies" section that summarizes the clinical trial results (i.e., evidence of prostate tissue ablation and the adverse event data), and states that the safety and effectiveness of the device in other clinical usages and patient populations have not been established;
- a summary of the physician training program:

    - a training course providing education on the procedure, transrectal ultrasound for HIFU, and post-HIFU recovery and care,
    - a didactic presentation, HIFU simulator training, and completion of at least five cases with a trained technician onsite, and
    - completion of at least five cases that are remotely monitored by a trained technician;
- statement that use of the Sonablate® 450 must be prescribed and administered under the direct supervision of a qualified and trained physician, after appropriate urologic patient evaluation;
- contraindication statements to avoid use of the device in patients in whom the benefits do not outweigh the risks, such as:
    - large (> 10 mm) cysts or calcifications in the planned ablation zone,
    - metal implants or stents in the urethra,
    - brachytherapy seeds in the planned ablation zone,
    - pre-existing inflammatory disease of the colon or rectum (such as proctitis or ulcerative colitis),
    - prior significant rectal surgery,
    - inability to insert or tolerate a transrectal ultrasound probe,
    - active urinary tract infection,
    - urethral stricture, and
    - latex allergy;
- warning and precaution statements to mitigate potential risks in the clinical setting, such as:
    - the Sonablate® 450 is not capable of ablating anterior prostate tissue > 4 cm from the transducer (due to physical limitations of the device);
    - in patients who have previously received radiation to the pelvic region, the Denonvillers' fascia should not be included within the targeted ablation zone, and the manufacturer's recommended values of total acoustic power should be followed;
    - the effectiveness of the device in treating any specific prostate disease has not been established;
    - the safety and effectiveness of the Sonablate® 450 have not been established in patients with the following conditions:
        - interest in future fertility,
        - bleeding disorders,
        - clinical or histological evidence of urinary bladder cancer,
        - renal impairment,
        - functional bladder problems, including neurological disorders that might affect bladder function,
        - post-void residual urine > 250 mL,
        - urinary retention requiring an indwelling catheter,
        - enlarged medial lobe of the prostate protruding into the urinary bladder,
        - clinical evidence of prostatitis within 6 months prior to HIFU,
        - bladder calculus, and
        - prostates > 40 cm^3.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the high intensity ultrasound system for prostate tissue ablation and the measures necessary to mitigate these risks.

Identified Risk	**Mitigation Measure**
Thermal injury from high intensity ultrasound exposure to non-target tissue: -erectile dysfunction -urinary incontinence -rectal fistula -osteomyelitis pubis	• Non-clinical performance testing • Software verification, validation, and hazard analysis • *In vivo* testing • Clinical testing • Labeling • Physician training
Thermal injury from high intensity ultrasound exposure to target tissue: -urethral stricture -bladder neck contracture -urinary retention -tissue debris/obstruction -voiding dysfunction -dysuria -hematuria -ejaculation disorder	• Clinical testing • Labeling • Physician training
Mechanical injury from unintentional movement of ultrasound components: -patient rectal injury -operator hand injury	• Software verification, validation, and hazard analysis • Clinical testing • Labeling • Physician training
Infection	• Sterilization validation • Reprocessing validation • Shelf life validation • Labeling
Electrical shock/Electromagnetic interference	• Electrical safety testing • Electromagnetic compatibility testing • Labeling
Adverse tissue reaction	• Biocompatibility testing

SPECIAL CONTROLS :

In combination with the general controls of the FD&C Act, the high intensity ultrasound system for prostate tissue ablation is subject to the following special controls:

(1) Non-clinical performance data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   (A) Characterization of acoustic pressure and power output at clinically relevant levels.

(B) Measurement of targeting accuracy and reproducibility of high intensity ultrasound output.
(C) Ultrasound-induced heating verification testing at target and non-target tissues.
(D) Electrical safety testing.
(E) Electromagnetic compatibility testing.

(2) Software verification, validation, and hazard analysis must be performed.
(3) The elements of the device that may contact the patient's mucosal tissue must be demonstrated to be biocompatible.
(4) Performance data must demonstrate the sterility of the device components that contact the patient's mucosal tissue.
(5) Performance data must support shelf life by demonstrating continued sterility of the device or the sterile components, package integrity, and device functionality over the identified shelf life.
(6) Performance data must support the instructions for reprocessing all reusable components.
(7) *In vivo* testing must demonstrate that the device thermally ablates targeted tissue in a controlled manner without thermal injury to adjacent, non-target tissues.
(8) Clinical testing must document the adverse event profile, provide evidence of prostatic ablation, and demonstrate that the device performs as intended under anticipated conditions of use.
(9) Training must be provided so that upon completion of the training program, the physician can:
(A) Use all safety features of the device;
(B) Accurately target the high intensity ultrasound energy within the desired region of the prostate;
(C) Perform the ablation procedure in a manner that minimizes damage to non-target tissues;

(10) Labeling must include:
(A) A section that summarizes the clinical testing results, including the adverse event profile and evidence of prostate ablation achieved.
(B) An expiration date or shelf life for single use components.

BENEFIT/RISK DETERMINATION

The risks of the device are based on the non-clinical laboratory studies, as well as data collected in a clinical study described above. The pivotal study indicated that nearly all (i.e., 99%) subjects experienced a HIFU application-related complication. Serious adverse events (SAEs) occurring in the population included urinary retention/obstruction (5%), hematuria (4%), rectal fistula (4%), urinary tract infection (4%), and osteomyelitis (3%). Non-serious adverse events primarily consisted of erectile dysfunction (71%), UTI (50%), urinary incontinence (leak) (47%), hematuria (43%), urinary retention (43%), urinary obstruction (20%), and urethral stricture (15%). The duration of a harmful event was dependent on the indication for prostate ablation and current disease status. Some of the harmful events such as voiding symptoms resolve on their own over weeks to months, and some such as infections resolve with medical therapies. Of the three patients with osteomyelitis, one patient underwent cystectomy and ileal conduit diversion. Some of the patients with urinary incontinence and erectile dysfunction resolve spontaneously over a period of months while a significant percentage have lifelong symptoms

requiring medical and surgical intervention. These include placement of an artificial urinary sphincter for treatment of incontinence and medications or devices for treatment of erectile dysfunction.

The probable benefits of the device are also based on the non-clinical laboratory studies as well as the data collected in a clinical study described above. For this *de novo*, effectiveness was defined as evidence that Sonablate® 450 ablates prostate tissue within the targeted region, as demonstrated by reductions in prostate volume and PSA level, and increase in the rate of negative biopsy, between baseline and 12 months post-HIFU. Ninety percent (90%) of the per-protocol population had a decrease in prostate size. The average reduction was approximately 50%. Across the entire population, 83% had a reduction in PSA at 12 months. Sixty-one percent (61%) of the intent to treat protocol population had a negative biopsy 12 months post-HIFU.

Additional factors to be considered in determining probable risks and benefits for the high intensity ultrasound system for prostate tissue ablation include:

- Robustness was enhanced by the use of objective endpoints for safety and documentation of tissue ablation. However, robustness was challenged by the reliance on a single-arm study and by missing data.
- It is likely that the device can ablate prostate tissue in a range of clinical settings.
- Post-radiation patients have limited options for removal or ablation of unwanted prostate tissue.
- The submission did not include patient perspective information; however, prior input from the advisory panel indicates that there is a low tolerance for risks since the majority of patients with this condition are currently observed.
- An extensive physician training program is in place to mitigate risks. Limitations in the labeling also mitigate risks.
- The technology is a novel strategy for ablating prostate tissue.
- The effectiveness of the device in ablating prostate tissue appears to be similar to that of existing methods, with comparable safety.

In conclusion, given the available information above, the data support that, for transrectal high intensity focused ultrasound (HIFU) ablation of prostatic tissue, the probable benefits outweigh the probable risks for the high intensity ultrasound system for prostate tissue ablation. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* for the high intensity ultrasound system for prostate tissue ablation is granted and the device is classified under the following:

Product Code: PLP
Device Type: High intensity ultrasound system for prostate tissue ablation
Class: II
Regulation: 21 CFR 876.4340