SPARED: FDA Update

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Office of Device Evaluation

Thursday, May 3, 2018

	Class I	Class II	Class III
Risk level	Low	Moderate	High
Sufficient information for controls?	General	General & Special	Insufficient
Premarket review?	Mostly exempt	510(k) De Novo	PMA
Examples	Tongue depressor, stethoscope	Endoscopes, infusion pumps	Cardiac ablation catheters, coronary artery stents

HIFU Premarket Submission History

- HIFU technologies considered Class III devices for the treatment of prostate cancer.
  - No predicate
    - PMA Pathway

HIFU Premarket Submission History

- Sonacare – Sonablate (January 2013)
  - Whole gland HIFU for post-EBRT prostate cancer
  - Achieve a PSA nadir ≤ 0.5 within 12 months and negative biopsy
- EDAP – Ablatherm (February 2013)
  - Whole gland HIFU for primary treatment of low risk prostate cancer
  - Achieve a PSA nadir ≤ 0.5 and stability of PSA by ASTRO criteria through 24 months without a positive biopsy

HIFU Premarket Advisory Panel

- Ablatherm (July 2014)
  - Vote: 8 against, 1 abstain
- Sonacare (October 2014)
  - 10 against, 1 abstain

- Safety data adequately documented.
- Did not demonstrate effectiveness for the intended population (localized CaP patients).
  - Lack of accepted endpoints to predict long-term clinical benefit.

“The Path Forward”

Indication for Use

- *“Sonablate* is indicated for the transrectal ablation of prostate tissue using high intensity focused ultrasound (HIFU).”
- “The Ablatherm® Integrated Imaging device is indicated for transrectal high intensity focused ultrasound (HIFU) ablation of prostate tissue.”

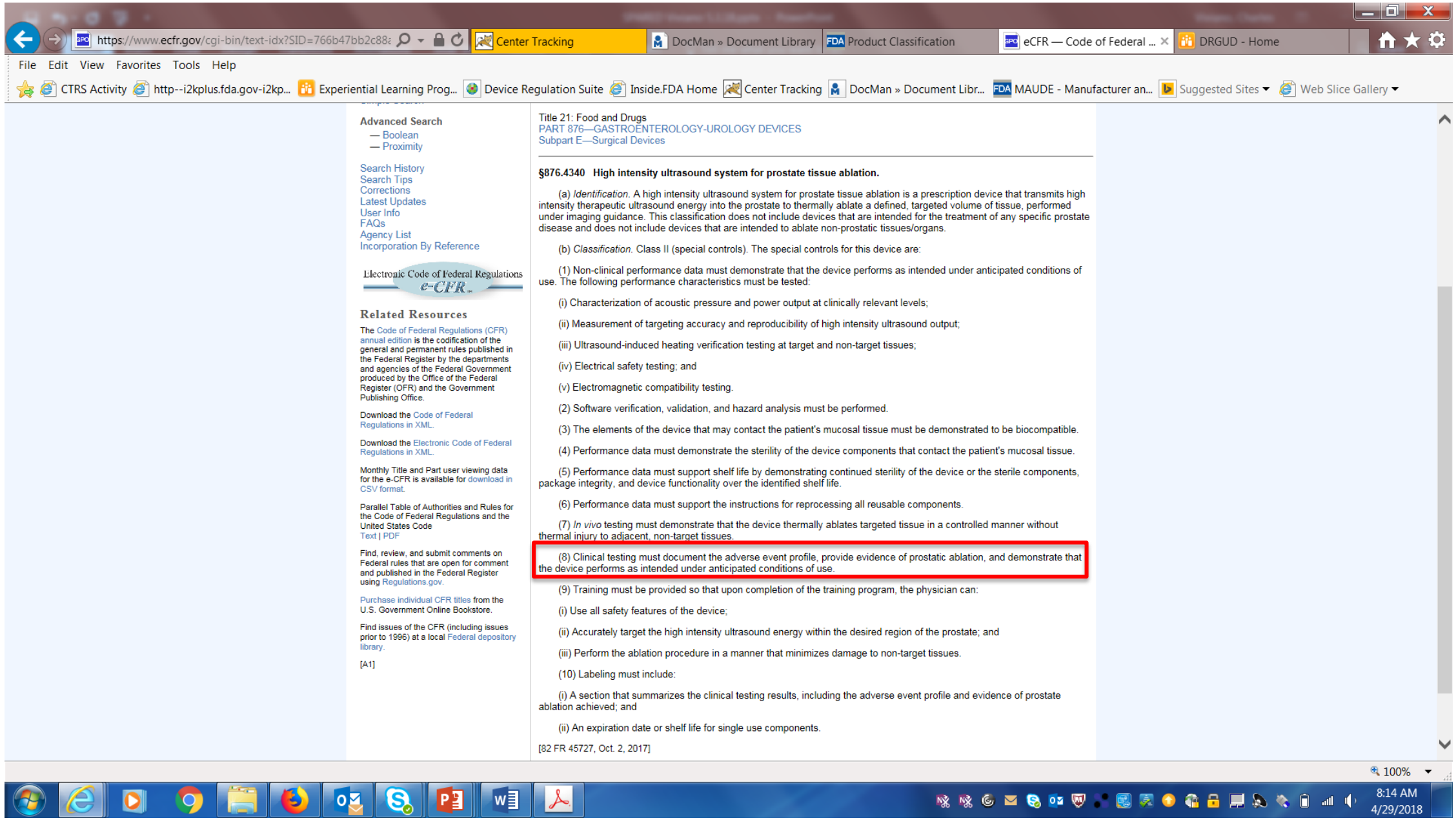
- *No indication for treating any specific disease of the prostate is provided!*
- *Manufacturers are limited to the labeling for the promotion of these devices.*

“The Path Forward”

- Prostate ablation endpoints identifiable and measurable:
  - Eradication of cancer on prostate biopsy;
  - Histology in a “treat-and-resect” study;
  - Reduction in PSA;
  - Reduction in prostate volume.
- Absence of ablation of non-target tissue (safety).

“The Path Forward”

- New risk-benefit perspective.
- FDA granted reclassification of the Sonacare HIFU device from Class III to Class II via the *De Novo* pathway (October 2015).
- EDAP HIFU device subsequently cleared via the 510(k) pathway using Sonacare as a predicate (November 2015).



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[A1]

Title 21: Food and Drugs
PART 876—GASTROENTEROLOGY-UROLOGY DEVICES
Subpart E—Surgical Devices

§876.4340 High intensity ultrasound system for prostate tissue ablation.

(a) *Identification.* A high intensity ultrasound system for prostate tissue ablation is a prescription device that transmits high intensity therapeutic ultrasound 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.

(b) *Classification.* Class II (special controls). The special controls for this device are:

(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:

(i) Characterization of acoustic pressure and power output at clinically relevant levels;

(ii) Measurement of targeting accuracy and reproducibility of high intensity ultrasound output;

(iii) Ultrasound-induced heating verification testing at target and non-target tissues;

(iv) Electrical safety testing; and

(v) 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:

(i) Use all safety features of the device;

(ii) Accurately target the high intensity ultrasound energy within the desired region of the prostate; and

(iii) Perform the ablation procedure in a manner that minimizes damage to non-target tissues.

(10) Labeling must include:

(i) A section that summarizes the clinical testing results, including the adverse event profile and evidence of prostate ablation achieved; and

(ii) An expiration date or shelf life for single use components.

[82 FR 45727, Oct. 2, 2017]

100%

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Premarket Data Requirements

- Effectiveness
  - Evidence of target ablation (12 months)
    - Prostate volume reduction
    - PSA reduction
    - Negative biopsy
    - Treat and resect
      - Secondary (IPSS)
  - Safety (12 months)
    - Evidence of non-target ablation
      - ALL adverse events
        - » ED (IIEF-5)
        - » UI (EPIC)
        - » Fistula, osteomyelitis

2018 FDA update- RWE

- FDA RWE guidance: when evaluating a RWE source on its fitness for regulatory purpose, the **quality** of the data as well as its **relevance** for the regulatory decision must be assessed.

- SPARED CRN “will support interim and long-term decisions as well as drive evidence-based guidelines” for regulators (e.g. FDA) and payers (e.g. CMS, private insurers) (Golan, 2018)

2018 FDA update- RWE

- **Based on DELPHI experts opinions, long-term endpoints**:
- post-ablation follow-ups on **PSA** testing, **imaging** and **biopsy** 6-12 months, and other **complications**
- to add additional **PRO**, e.g. treatment satisfaction, posttreatment regret, whether appropriate counseling was provided
- To add other minimum core elements from **other ablation technologies.**

Other PRO: e.g. EPIC-CP (Expanded Prostate Cancer Index Composite for Clinical Practice) to predict 2-year post-prostatectomy sexual outcomes (Chipman, 2014)

A word about PROs …

- They should be validated.
- It's helpful if Minimal Clinically Important Differences (MCID) are identified.

Patient Engagement Study

CDRH Strategic Priority of Partnering with Patients

"Increase use and transparency of patient input as evidence in our decision making."

❖ HIFU Patient Preference Study:

- Background: HIFU treatment benefit-risk balance is unclear for patients with prostate cancer. Adverse event profile known but no data on oncologic outcomes.

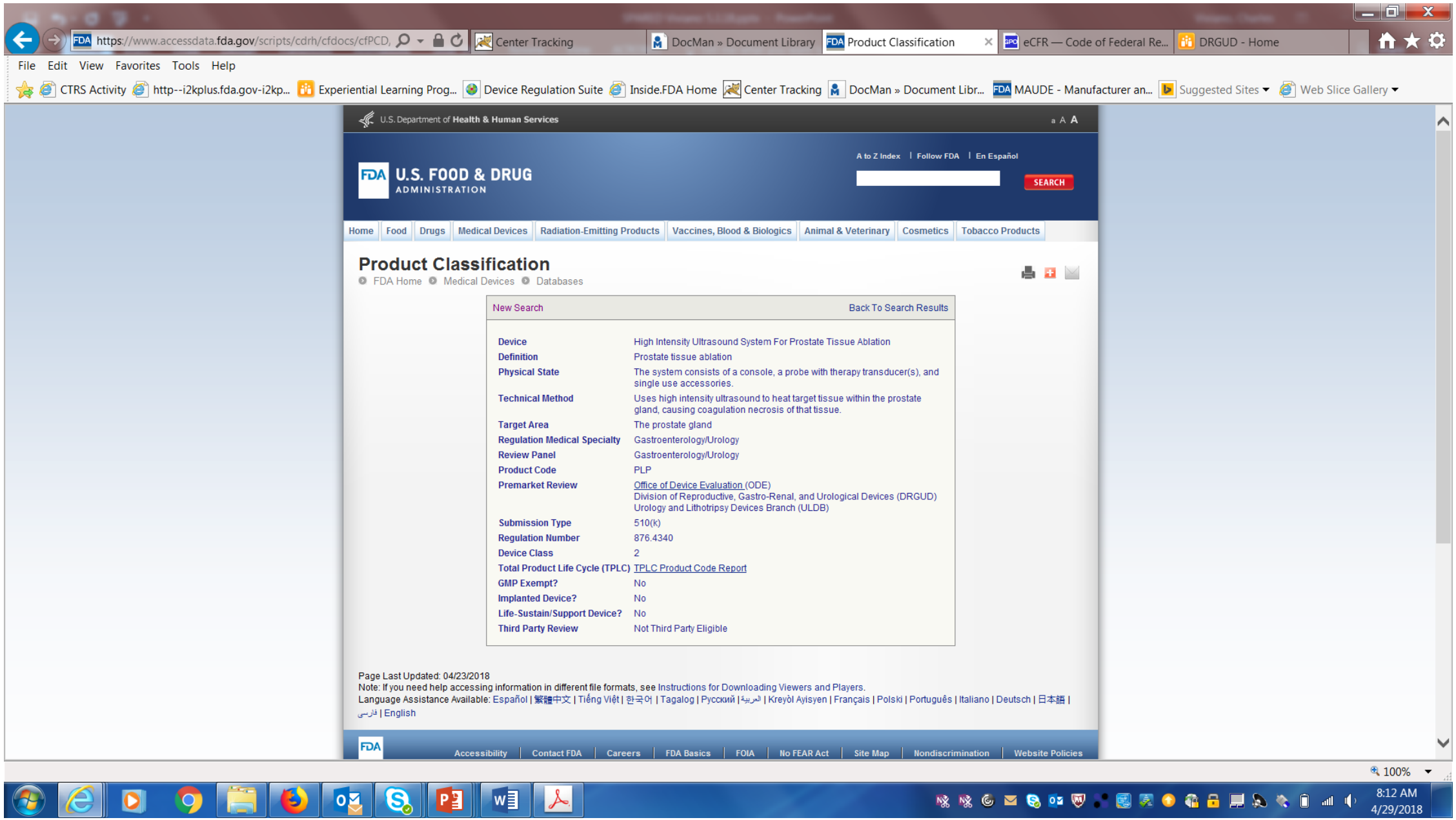
- **Method**: Administer preference surveys (We are still recruiting!)
  - UMD, Cornell, JHU, UCSF
- **Outcome**: Gain patient perspective on benefit–risk tradeoff associated with HIFU to

1. Inform future premarket device evaluation of ablation tools.
2. Deliver better ablation devices sooner to patients.

Patient Recruitment or for more info: Joyce Lee

PcaStudy@fda.hhs.gov

Thank you!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Device: High Intensity Ultrasound System For Prostate Tissue Ablation
Definition: Prostate tissue ablation
Physical State: The system consists of a console, a probe with therapy transducer(s), and single use accessories.
Technical Method: Uses high intensity ultrasound to heat target tissue within the prostate gland, causing coagulation necrosis of that tissue.
Target Area: The prostate gland
Regulation Medical Specialty: Gastroenterology/Urology
Review Panel: Gastroenterology/Urology
Product Code: PLP
Premarket Review: Office of Device Evaluation (ODE)
Division of Reproductive, Gastro-Renal, and Urological Devices (DRGUD)
Urology and Lithotripsy Devices Branch (ULDB)
Submission Type: 510(k)
Regulation Number: 876.4340
Device Class: 2
Total Product Life Cycle (TPLC): TPLC Product Code Report
GMP Exempt?: No
Implanted Device?: No
Life-Sustain/Support Device?: No
Third Party Review: Not Third Party Eligible
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