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# **REDUCING REGULATORY BARRIERS TO FOCUSED ULTRASOUND TECHNOLOGY**

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**STRATEGIES FOR THE FOCUSED ULTRASOUND FOUNDATION**

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*On my honor as a student I have neither given nor received unauthorized aid on this assignment*

A handwritten signature in cursive script, reading "Liz Dobuz".

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## EXECUTIVE SUMMARY

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The U.S. Food and Drug Administration (FDA) has automatically classified focused ultrasound (FUS) devices Class III, which requires sponsors to demonstrate the safety and effectiveness of a device through clinical trials. This requirement adds significant time and cost to the device development process; reclassification to Class II would be highly beneficial for the future of FUS. Statute outlines two strategies for reclassifying FUS to a class with lower regulatory standards: filing a petition for reclassification based on new information and filing a *de novo* application to request a risk-based review of a novel technology. There are three additional options for FUS Foundation action with less direct effects on reclassification: creating grants for regulatory science, educating stakeholders about FDA, and increasing direct-to-FDA advocacy. Each of these options and alternatives is assessed based on its likelihood of achieving success, time to success, and cost to the Foundation. Ultimately, this analysis recommends that the FUS Foundation take no statutory action to reclassify FUS at this time, and initiate efforts to increase Foundation stakeholder understanding of FDA regulations and their impact on the future of FUS.

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# INTRODUCTION

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For many years, U.S. federal law has worked to assure patients and doctors that approved drugs and medical devices are safe and effective for their intended use<sup>1</sup>. U.S. Food and Drug Administration (FDA) regulation helps to address difficulties that ill patients face in making informed decisions about these products, and provides a remedy for the market failure that would otherwise result from asymmetric information.

FDA regulation means, however, that products cannot be marketed without FDA approval or clearance, leading to instances where certain technologies and products appear to be safe and effective yet are unavailable to patients who could benefit from them. This situation applies to focused ultrasound (FUS) technology, which harnesses ultrasonic energy to create non-invasive therapeutic thermal or mechanical disturbance in tissues.

FDA's current scheme for reviewing FUS technologies creates a barrier for U.S. access to FUS treatments. The rigorous application process leaves researchers searching for clinical trial funding from sources like the FUS Foundation, and increases the time from discovery of a new treatment to availability of this treatment for U.S. patients. The FUS Foundation describes itself as "a unique medical research, education, and advocacy organization created as the catalyst to accelerate the development and adoption of focused ultrasound by streamlining the process and overcoming barriers<sup>2</sup>, so the Foundation should consider new approaches to overcoming this FDA classification barrier.

## FUS TECHNOLOGIES

Focused ultrasound devices focus converging beams of ultrasound energy on small targets deep in the body<sup>3</sup>. This concentration of energy raises tissue temperature at the focal point, with a goal of causing cell death. Magnetic resonance guided FUS uses magnetic resonance imaging (MRI) to plan treatment in advance and monitor temperature changes from ablation in real-time<sup>4</sup>. Computer software uses these images to establish a treatment plan with precise targeting from a focused ultrasound transducer, which is

housed in acoustically transparent fluid inside a patient table with a specialized cradle<sup>4</sup>. Precise motors in the table move the transducer during treatment based on the computer-generated treatment plan, while the operator monitors the treatment from a workstation.

Currently, only treatments for bone cancer metastases and uterine fibroids are available in the United States. Researchers and device-makers in the U.S. are working to increase the number of FUS treatments available to U.S. patients in the near future, but they must first receive FDA approval for these new applications. The European Union has approved use of FUS technologies to treat many different conditions, including treatments for neurological, musculoskeletal, oncological, cardiovascular, and gynecological conditions<sup>3</sup>.

Clinical trials and adverse event reports have noted some important risks of the technology, including damage to non-target tissue and skin burns. Clinical trials for the uterine fibroid device found that 8 patients suffered temporary internal nerve damage from far-field heat, though all but one of these cases was resolved within three days<sup>5</sup>. Patient movement can also result in ablation of the incorrect tissue, which occurred in two adverse event cases reported to FDA. Patients suffered from bowel perforation by the FUS treatment; the event was attributed to user error, since the operator should have adjusted the treatment plan after the patient moved. Clinical trial reports also cite skin irritation and burning at the site of application; five patients in the uterine fibroid pivotal trial experienced first or second-degree skin burns<sup>5</sup>, and one patient in the bone metastases pivotal trial experienced a 3 cm third degree burn<sup>6</sup>.

## **REGULATORY CONTROLS AND DEVICE CLASSIFICATION**

FDA classifies devices into three classes based on both their relative risks to patients and the regulatory controls necessary to provide a reasonable assurance of safety and effectiveness. FDA then assesses these devices based on their intended use, technological characteristics, and evidence that a device is safe and effective to decide whether the device can be marketed in the U.S.

## ***Intended Use and Indications***

Devices are all regulated with consideration for their intended use, which is the general purpose or function of a device<sup>7</sup>. Within a device’s intended use is its indication for use, which is the disease or condition that the device treats, prevents, cures, or mitigates and the types of patients who should use the device. Changes in indications, such as changing from an aesthetic indication to a therapeutic indication, changing the anatomical structure, or changing the target population, could lead to creation of a new intended use for a device if these changes raise different questions of safety and effectiveness.

### ***Class I***

Class I devices present minimal potential for harm to the user<sup>i</sup>. This class includes simple devices like examination gloves, bedpans, tongue depressors, and some hand-held surgical instruments. These devices are subject to general controls, which can include requirements for device registration with FDA, proper labeling and branding, good manufacturing practices, and notification of repair, replacement, or refund.

### ***Class II***

FDA classifies moderate-risk devices in Class II. FDA “clears” these devices after reviewing a Premarket Notification, which is commonly referred to as a 510(k). FDA compares the intended use and technology of a device to a “predicate”, which must be a Class II device that is already legally marketed in the U.S.<sup>ii</sup>.

Class II devices are subject to both general controls and special controls<sup>iii</sup>. Special controls are tailored to the unique characteristics and risks of a device type to provide reasonable assurance of safety and effectiveness. These controls generally include performance standards, postmarket surveillance, patient registries, special labeling requirements, and premarket data requirements; device-specific requirements for

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<sup>i</sup> 21 U.S.C. § 360c(a)(1)(A)

<sup>ii</sup> 21 C.F.R. § 807.92(a)(3)

<sup>iii</sup> 21 U.S.C. § 360c(a)(1)(B)

laboratory tests, electrical specifications, biocompatibility testing, material composition, and guidelines for appropriate clinical testing are also common<sup>8</sup>. FDA and manufacturers leverage their understanding of the risks associated with the device to design these special controls, so devices in Class II generally have well-understood risks and benefits.

A new device is deemed “substantially equivalent” to its predicate if it has the same intended use and has either the same technological characteristics or slight differences in technological characteristics that do not raise additional questions of safety and effectiveness<sup>iv</sup>. Manufacturers must identify the risks and benefits of their product and demonstrate that the special controls created for the predicate device are sufficient for assessing and controlling the risks of their new product. If the manufacturer can demonstrate that their device is substantially equivalent to the predicate, then the FDA will clear the device for marketing as long as the manufacturer complies with the general and special controls.

### ***Class III***

Devices are classified into Class III because they are high risk. These are devices that “support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury”<sup>9</sup>. FDA requires sponsors of Class III devices to submit a Premarket Approval (PMA)<sup>v</sup>. A PMA requires device sponsors to demonstrate that their device is safe and effective for its intended use<sup>10</sup>. They demonstrate this through a series of carefully designed clinical trials, which take up to ten years to complete.

There are significant time-savings from receiving a Class II classification rather than Class III, from both the lack of clinical trial requirement and differences in FDA review. 510(k) applications generally do not require clinical testing beyond

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<sup>iv</sup> 21 U.S.C. § 360e(3)(C)(i); "Different technological characteristics" is defined in section 513(i)(1)(B) of the FD&C Act as "a significant change in the materials, design, energy source, or other features of the device from those of the predicate device."

<sup>v</sup> 21 U.S.C. § 360e . Although the large majority of Class III devices are approved through PMA, there are still some Class III devices that were cleared using a 510(k) before the 1976 amendment. FDA intends to reclassify these “preamendment devices”

demonstration of substantial equivalence, whereas PMA applications require studies to prove safety and effectiveness. PMA application reviews take longer to receive FDA approval than 510(k) reviews. The Government Accountability Office reported that PMAs filed in 2008 took an average of 627 days from the day of first filing to receive a decision, whereas 510(k) applications in the same period took an average of 161 days<sup>11</sup>. The time savings from Class II relative to Class III are significant.

### ***Proposed Changes: March 2014***

FDA proposed changes to its definitions of the three classes on March 25<sup>th</sup>, 2014<sup>12</sup>. Notably, the proposed rule ties Class II designation directly to FDA's ability to generate a special controls document for the device. It subsequently changes the definition of Class II to include devices that are deemed high risk, but FDA is confident that special controls it designs will provide a reasonable assurance of safety and effectiveness. This proposed rule also makes it easier to reclassify an entire product code, rather than petitioning for reclassification of certain devices within the code. This document signals a general willingness on FDA's part to address concerns of stakeholders, and move to a more risk-based approach for classification than the current "substantial equivalence" standard.

### ***Initial Classification of Devices***

All new medical devices are automatically classified into Class III without a formal rulemaking process. These devices remain in Class III, unless and until:

- FDA issues an order finding the device substantially equivalent to a predicate device,
- The device sponsor successfully proposes special controls that provide a reasonable assurance of safety and effectiveness in a *de novo* application,
- A Classification Panel decides to reclassify a device or device type based on new information, and FDA issues an order reclassifying the device to Class I or II<sup>9</sup>.

## **FDA CLASSIFICATION OF FUS**

FDA has automatically classified Focused Ultrasound devices into Class III<sup>vi</sup>, and has approved two devices for fairly narrow indications<sup>13</sup>. The device type, “Ablation System, High Intensity Focused Ultrasound (Hifu), Mr-Guided,” is represented by the product code “NRZ”, and considered under the Radiology classification panel<sup>13</sup>.

Though both indications for FUS are categorized under the “NRZ” product code, their paths to approval were quite different. FDA approved ExAblate 2000 for “ablation of uterine fibroid tissue in pre- or peri-menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure, have a uterine size of less than 24 weeks, and have completed child bearing” in 2004<sup>14</sup>. In its press release about ExAblate’s 2004 approval, FDA wrote “this is the first time [FUS and MRI] have been combined and the first time MRI has been used to monitor tissue temperature”<sup>15</sup>.

In 2012, FDA approved the ExAblate 2000/2001 system for pain palliation of metastatic bone cancer in “patients 18 years of age or older who are suffering from bone pain due to metastatic disease and who are failures of standard radiation therapy, or not candidates for, or refused radiation therapy”<sup>16</sup>. The device was approved through an expedited review because the device “addresses an unmet medical need, and is intended to treat a condition that is life-threatening and is irreversibly debilitating”<sup>17</sup>. The agency decided that “the treatment benefits of the device for the target population outweigh the risks of diseases when used in accordance with the directions for use”<sup>17</sup>. Notably, the target population was already at significant risk of injury or death because of their underlying disease, and FUS treatment was used as a last-resort option for pain palliation rather than treatment of the metastases.

### ***FDA Regulation of Similar Technology***

A search for the term “ablation” in FDA’s device classification database reveals 12 different product codes, representing a variety of different device types such as cardiac

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<sup>vi</sup> The device type has no regulation number, which indicates that FDA did not issue a formal order to classify the devices into Class III. Thus, the current classification is automatic and not final.

catheters and devices for treatment of atrial fibrillation<sup>18</sup>. Other devices that use energy for thermal ablation are classified into Class II, but FDA does not consider these devices to be predicates for therapeutic FUS (see Appendix A). Devices associated with ablation are divided into highly specific categories based on their technological characteristics and intended use. For example, FDA regulates devices like laser ablation systems, which rely on probes to deliver energy to specific points in the brain or rest of the body<sup>19</sup>, separately from external beam radiation devices like the CyberKnife or Gamma Knife, both of which are Class II under product code IWB<sup>20</sup> and use focused beams to deliver precise radiation to small targets in different areas of the body.

Though use of MRI thermometry was novel in 2004, its use in ablation surgeries has increased and is currently incorporated into 510(k) clearances. For example, Class II devices like the Visualase Thermal Therapy System (cleared in 2007) use MRI to measure relative changes in temperature from laser ablation<sup>21</sup>, and the Monteris AutoLITT (cleared in 2009) and NeuroBlate (cleared in 2011) systems use real-time MRI thermometry to guide surgery<sup>19</sup>.

The concept of using energy to ablate tissue predates the 1976 Medical Device Amendments, which has significant effects on the way many devices are regulated<sup>22</sup>. Any device that was legally marketed before May 28, 1976 and has neither been significantly modified or become subject to PMA approval is termed a “preamendment device”<sup>23</sup>. These devices were “grandfathered” into the market without additional regulations, as long as the device still has the same intended use and technological characteristics as it did in 1976<sup>24</sup>. If the intended use changes, then the new device becomes subject to 510(k) clearance<sup>23</sup>. For example, a precursor to modern Radiofrequency (RF) Ablation called the Bovie Knife was available in 1928 for cauterizing or cutting tissue<sup>22</sup>. Since RF Ablation devices were available before 1976, updates to the designs or indications are subject to 510(k) clearance, rather than PMA.

Additionally, these early devices benefitted from very general definitions of indications. A lawyer who specializes in medical device regulation stated that indications have generally become specific over time, and a former FDA official confirmed

specifically that indications for RF Ablation have changed from an indication for ablation of soft tissue to present-day indications for specific applications in the heart, for example.

### ***Why is FUS in Class III?***

Though clinical trials for the uterine fibroid indication were overall positive, FDA is unlikely to classify a new device into Class II unless there is a clear predicate or FDA is confident that it can design special controls for the device. In absence of these requirements, devices are automatically classified into Class III.

Predicate devices must have the same intended use and technological characteristics as the new device. FDA distinguishes between types of energy in its device types, so focused ultrasound would not be considered technologically similar to radiofrequency ablation, laser ablation, cryoablation, or types of stereotactic radiosurgery. Additionally, FDA reported that there were no predicates for MRI thermometry in 2004 since it was the first time MRI was used to monitor temperature.

A former high-level FDA official stated that FDA prefers to wait until it has received multiple PMAs that provide a similar understanding of the risks and benefits of a device before reclassifying into Class II and writing special controls. Each application represents a single indication with a single PMA of clinical trial data rather than the multiple trials and indications that they prefer before making a decision. With only two indications for FUS currently approved, there is a need for more applications to demonstrate safety and effectiveness of FUS devices, as well as innovative special controls to manage the risks.

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## ALTERNATIVES & OPTIONS

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FDA has automatically classified FUS in Class III, but this classification is not final; at some point, FDA will formally classify devices under the NRZ product code, likely into Class II or Class III. The FUS Foundation can take action to accelerate achievement of Class II through “statutory alternatives,” which are explicitly explained in FDA regulation, and “soft options,” which are actions that the FUS Foundation could take immediately to accelerate reclassification.

### “STATUTORY” ALTERNATIVES

Statute clearly outlines the two alternative paths to reclassification of devices: *de novo* review or reclassification. The FUS Foundation could take steps to initiate these two processes itself, or wait for industry action. Thus, there are three “statutory alternative” actions that the FUS Foundation could take to achieve reclassification of FUS:

- Wait for Industry Action
- Sponsor a *De Novo* Application
- Prepare and File a Petition for Reclassification

#### ***Wait for Industry Action***

Typically, companies work with regulatory consultants to initiate reclassification. This is a well-established pathway towards reclassification, so the FUS Foundation could rely on the FDA to signal their willingness to consider reclassification to companies rather than facilitating the process themselves. In some cases, like in the 2014 reclassification of shortwave diathermy for all other uses, companies with similar products formed a coalition to present a petition to the FDA<sup>25</sup>.

#### ***Encourage or Sponsor a De Novo Application***

The FUS Foundation could encourage a company to file an application for *de novo* review of a new device through sponsoring a regulatory consultant to prepare the application. Hypothetically, the Foundation could initiate the process immediately, but

the process of finding an appropriate device to sponsor and company to work with could be lengthy.

The *de novo* process offers sponsors an opportunity to request a risk-based classification for the device rather than relying on an assessment of substantial equivalence alone. Before creation of the *de novo* process in 1997, the only mechanism to avoid an automatic Class III designation was to file a successful 510(k) establishing substantial equivalence. Thus, some innovative low to moderate risk devices were deemed “not substantially equivalent” and placed in Class III despite relatively low risk profiles<sup>26</sup>. Now, sponsors can submit a *de novo* application that identifies the risks and benefits of the device, as well as general and special controls that they believe would provide a reasonable assurance of safety and effectiveness. Since June 2012, sponsors can submit a *de novo* application without first filing an unsuccessful 510(k), though the *de novo* application requires information that is traditionally filed in a 510(k)<sup>27</sup>.

In a *de novo* application, the sponsor must demonstrate that the device is low or moderate risk, and propose special controls that address these risks if the device is more appropriate for Class II<sup>26</sup>. Thus, *de novo* applications often require more extensive clinical testing than 510(k) applications because the sponsor has to demonstrate the logic behind their proposed controls and support their proposal with data, rather than establishing substantial equivalence alone.

A device that is successfully classified into Class II through the *de novo* process could serve as a predicate for future devices. Thus, the *de novo* approval could establish an entirely new device type in Class II if the special controls are well designed and the device’s indication is widely applicable to different FUS devices.

### ***Prepare and File a Petition for Reclassification***

The Focused Ultrasound Foundation could petition the FDA to reclassify therapeutic focused ultrasound based on new information. This information must be publicly available and FDA must be confident that this information can be used to design special controls (see Appendix B & C).

FDA accepts petitions from “an interested person,” who must provide scientific evidence to support FDA’s determination that safety and effectiveness can be assured through less stringent controls<sup>28</sup>. Provisions in the Food and Drug Administration Safety and Innovation Act (FDASIA) changed reclassification from requiring a regulation to requiring an administrative order, which decreases the amount of time and effort FDA must expend to reclassify a device<sup>28</sup>. It must now publish an order in the Federal Register that summarizes the data in the petition, convene a classification panel of subject-matter experts to consider the request, and entertain public comments from the Federal Register notice.

The Focused Ultrasound Foundation could leverage its contacts with different stakeholders to file a petition for reclassification. It is capable of pulling together studies from different countries, different companies, and different universities to present a complete data package, rather than relying on a single company to present its case. Though reclassification requests from Foundations or advocacy groups is rare, it is not unprecedented; the Orthopedic Surgical Manufacturers Association (OSMA) played a similar role in 2011 when it sponsored classification of a posterior cervical screw fixation into Class II<sup>29</sup>.

## **OTHER OPTIONS**

In addition to the three statutory alternatives, there are four options for actions that the Focused Ultrasound Foundation could take immediately to accelerate reclassification:

- Maintain Current Funding and Support Efforts
- Offer Grants for FUS-related Regulatory Science
- Encourage Stakeholder Understanding of FDA Regulation
- Increase Direct-to-FDA Advocacy Efforts

The goal of these options is to increase FDA understanding of FUS risks and benefits so that the agency feels confident designing special controls in the future.

### ***Maintain Current Funding and Collaboration Efforts***

Currently, the Focused Ultrasound Foundation spends a large portion of its budget on funding clinical trials. Grants provide support for researchers in the latest stages of animal testing or initiating their first human clinical trial to better facilitate transfer of promising laboratory devices or techniques to human clinical use, and FUS Fellowships ensure that researchers can continue to focus on this area.

The Foundation also organizes a biennial conference, which serves as a hub for dialogue and collaboration about Focused Ultrasound technology and research. The Focused Ultrasound Foundation could continue to facilitate progress in science, technology, and engineering, while allowing medical device companies to consider regulatory issues individually.

### ***Offer Grants for FUS-related Regulatory Science***

The FUS Foundation could expand its grant program to support research on regulatory science that may lead to FUS-specific special controls. Regulatory science focuses on developing tools and procedures for assessing the safety and effectiveness of products. The National Institutes of Health (NIH) initiated a grant program in 2010 to sponsor regulatory science, and partnered with FDA and the Defense Advanced Research Projects Agency (DARPA) to increase government investment in regulatory science<sup>30</sup>. FUS has benefitted from this partnership through research out of a laboratory at FDA that studies regulatory science for ultrasound applications, including high-intensity focused ultrasound. This laboratory has developed a synthetic tissue substitute for testing<sup>31</sup> and computational models for assessing the safety and effectiveness of FUS devices<sup>32</sup>. Further regulatory science research, conducted either inside or outside FDA, could develop FUS-specific tests to address FDA concerns about risks when designing special controls.

### ***Encourage Stakeholder Understanding of FDA Regulation***

The FUS Foundation has many stakeholders, including device companies, researchers, clinicians, patients, and donors. Encouraging understanding of FDA regulation among these stakeholders could lead to more constructive relationships with

the agency, as well as increased understanding of the types of actions that these groups can take to facilitate faster approval and eventual reclassification.

Strategies to increase stakeholder understanding could include:

- Sponsor webinars or seminars to explain device regulation and the current situation for FUS
- Feature big-name regulatory connections as speakers at future Symposia
- Consider regulatory pathways as a factor when discussing future applications of FUS at Symposia

FDA approval is a key step in achieving widespread use of FUS in a clinical setting. Thus, it would be beneficial to all companies and interested parties to have a basic understanding of FDA regulation, and the types of hurdles that FUS needs to surmount before it can be fully integrated into clinical settings. One way to achieve this is by offering a one-hour “all you need to know about the FDA” seminar, either at the symposium or at another time, to ensure that companies understand the logic behind FDA regulations. This presentation could signal that the FUS Foundation is aware of regulatory challenges surrounding FUS, and is willing to offer a helping hand to groups struggling with these challenges. This could also be an opportunity to gauge support for expansion of FUSF attention to regulatory issues.

One goal of the 2014 symposium is identification of future applications of FUS that maximize near-term value. FDA approval is an important component of rapid commercialization, and it will be important to consider the regulatory framework when deciding next steps, particularly since FDA is sensitive to subtle differences in indications. Discussing how device indications for use work, and strategizing about future applications of FUS with an eye towards achieving broader indications could be extremely beneficial to the industry.

### ***Increase Direct-to-FDA Advocacy Efforts***

In order for FDA to reclassify FUS, the agency must be convinced that it knows enough about the risks and benefits of the device to design appropriate special controls. Continuing efforts to reach out to FDA officials for attendance at the symposium and

organizing educational seminars at FDA will ensure that FDA is familiar with FUS and the types of risks and benefits the technology presents.

FDA regulations and interpretations of statute are constantly evolving and changing. If the Foundation decides to engage in regulatory issues, it should demonstrate that it is keeping up with these changes and thinking critically about how this evolution affects FUS. FDA publishes changes to regulations for public viewing, and will consider comments from stakeholders when they make a final decision on the regulation. One way to demonstrate a commitment to advocacy for FUS is by writing public comments on proposed rules issued by FDA in the Federal Register. For example, preparation of a comment for proposals like the March 25<sup>th</sup> rule would not only give FUS Foundation stakeholders a voice, it would show that the Foundation is knowledgeable enough to think critically and constructively about FDA decision-making.

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## CRITERIA

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There are three criterion that the FUS Foundation should consider when deciding on future actions towards reclassification of Focused Ultrasound.

- Likelihood of Success
  - Understanding risks and benefits of FUS
  - Achieving reclassification to Class II
- Time Required
  - Implementation
  - “Lag time” before initiating reclassification efforts
- Cost to FUS Foundation

The first criterion for evaluating the four alternatives is the likelihood of success. The ideal outcome from any FUS Foundation action would be increased understanding of FUS risks and benefits in the short-run, with a long-term goal of achieving Class II classification for all FUS devices.

The next criterion is the time it will take to implement different strategies and the “lag time” before achieving Class II. This criterion takes into account the time for FUS Foundation preparation and implementation of each option. Appropriate timing of FUS Foundation action is critical, so it is also helpful to consider how much “lag time” there will be before achieving the best chance for success.

The last criterion is the cost to FUS Foundation. This cost is characterized in terms of funds directly spent on different initiatives and hiring experts.

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## **EVALUATION: STATUTORY ALTERNATIVES**

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All options and alternatives are assessed using relevant criteria. Statutory alternatives do not advance efforts to understand the risks of FUS, and thus are not assessed on this factor. Likelihood of success is represented in terms of high, medium, or low, and other criteria are represented by figures determined in the literature or in conversations with experts.

### **LIKELIHOOD OF SUCCESS**

#### ***Wait for Industry Action***

Though this alternative represents a passive position for the FUS Foundation, it is important to note that reclassification is inevitable since FDA has not formally classified FUS<sup>vii</sup>. Since similar devices are classified in Class II, the likelihood that FUS will eventually be reclassified into Class II, even if the FUS Foundation does not coordinate or initiate the process, is high.

#### ***Encourage or Sponsor a De Novo Application***

A *de novo* application has a low chance achieving classification of FUS into Class II. The process was created for novel devices, yet FDA has already approved FUS

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<sup>vii</sup> Though FDA could formally classify FUS into Class III, it is unlikely that this will occur based on classifications of similar technologies and the high-risk profile of other Class III devices.

devices and automatically classified them into Class III. The process was also created for low to moderate risk devices, and the FDA is unlikely to agree that a new FUS device fits this risk profile unless there is highly convincing new evidence showing that the device sponsor has identified the risks and can create a special controls document. For example, FDA approved a *de novo* application for aesthetic use of focused ultrasound in 2011<sup>33</sup>. This system uses FUS to stimulate superficial tissue, and does not require the precision that therapeutic FUS requires. It is clear that this device is lower risk than therapeutic FUS, which seems to demonstrate that therapeutic uses of FUS are unlikely to qualify for the *de novo* process.

### ***Prepare and File a Petition for Reclassification***

The likelihood of achieving Class II would be very high if FUS Foundation took the lead on preparing and filing a petition for reclassification. This is because the FUS Foundation can act as a neutral third party to facilitate cooperation between otherwise competitive companies. The FUS Foundation has also formed relationships with regulatory consultants, who could either prepare the reclassification petition or recommend the best consultant for the job. A current regulatory consultant explained that reclassifications are so rare<sup>viii</sup> that most consultants only complete one petition in their entire careers, if any. Leveraging connections in the industry to find experts who are highly qualified to prepare a successful application will increase the likelihood of achieving Class II designation for FUS.

## **TIME REQUIRED**

### ***Wait for Industry Action***

Reclassification will not succeed unless companies can prove that they understand the risks and can control for risks using special controls. A former FDA official estimated that FDA expects similar results from 4-7 clinical trials for similar indications before a device can be reclassified. This same official also estimated the number of years it would

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<sup>viii</sup> FDA estimates that there will be 6 reclassifications a year<sup>34</sup>, in contrast to over 2,000 annual 510(k) clearances<sup>24</sup>.

be before FDA reclassifies FUS based on his experience at FDA and working as a consultant for the industry, and concluded that it would likely be 20 years before industry came together to work towards reclassification.

FDA estimates that the reclassification process itself takes 497 hours, which is over one year assuming that there is one person working on the application for 8 hours a day, 5 days a week<sup>12</sup>. FDA based this number on “estimates by FDA administrative and technical staff who are familiar with the requirements for submission of a reclassification petition, have consulted and advised manufacturers on these requirements, and have reviewed the documentation submitted”<sup>12</sup>.

### ***Encourage or Sponsor a De Novo Application***

A *de novo* application would be most successful if it represented a unique device that cannot be directly compared to other Class III applications of FUS. Delaying the application too long will likely mean more Class III FUS devices, which will make the new device seem less novel. Thus, the necessary lag time before a *de novo* application is relatively short compared to reclassification, and only accounts for the amount of time it will likely take to find an appropriate device and complete clinical trials.

FDA estimates that the process of preparing a *de novo* application is 100 hours, or 2.5 weeks if one person works on the application 8 hours a day for 5 days a week<sup>26</sup>.

### ***Prepare and File a Petition for Reclassification***

The FUS Foundation could speed up the timeline for reclassification by taking a leadership role and facilitating cooperation within the industry. The FUS Foundation would initiate this process before the companies would otherwise act, so the lag time to reclassification may decrease to 15 years.

FDA estimates that the reclassification process itself takes 497 hours, which is over one year assuming that there is one person working on the application for 8 hours a day, 5 days a week<sup>34</sup>.

## **COST TO FUS FOUNDATION**

### ***Wait for Industry Action***

Waiting for industry to initiate a reclassification petition would not require any direct FUS Foundation expenditures.

### ***Encourage or Sponsor a De Novo Application***

FDA estimates that each *de novo* application costs \$15,000, assuming that the fee for preparation is \$150 per hour<sup>26</sup>. However, a current regulatory consultant indicated that fees realistically range from \$200 to \$700 per hour, which would result in a maximum total cost of \$70,000 for the application. At this time, the *de novo* application does not require a user fee, so the only cost associated with the application is preparation. It is likely that the application will require significant clinical data to support it, and the FUS Foundation could potentially support some portions of these trials. This analysis takes neither this potential funding into account, nor the FUS Foundation staff hours required to coordinate this plan, so the estimate reflects only the future cost to the FUS Foundation of sponsoring the application<sup>ix</sup>.

### ***Prepare and File a Petition for Reclassification***

FDA estimates that each reclassification petition costs \$75,000 assuming a per-hour cost of \$150<sup>34</sup>. However, reclassifications are rare and require special expertise that will likely come at a high per-hour cost. Assuming a per-hour cost of \$700 yields a total cost of \$348K for the application alone. At this time, there is no user fee associated with reclassification. This analysis does not account for the FUS Foundation staff hours required to coordinate this plan.

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<sup>ix</sup> This analysis also assumes that the Foundation will fund the entire application, rather than simply providing a portion of the total cost.

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## EVALUATION: OTHER OPTIONS

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Other options for FUS Foundation action are assessed relative to the baseline of the Foundation's current actions. Thus, qualitative options are reported using high, medium, and low increase or decreases relative to the baseline.

### LIKELIHOOD OF SUCCESS

#### *Maintain Current Funding and Support*

Though maintaining current funding and support may seem like inaction, this funding actually facilitates development of new technologies by funding researchers and clinical trials. These trials will help understand the risks associated with devices, and increasing the rate of FUS technology development will result in more successful PMAs. Thus, maintaining the status quo will have a positive impact on the likelihood of understanding all risks of FUS.

#### *Offer Grants for FUS Regulatory Science*

Offering a new grant for regulatory science research could accelerate identification of risks significantly. The tools and tests developed through these grants could speed up the development of special controls for FUS devices, which is a requirement for reclassification. However, this option will only have this highly positive effect if researchers are interested in the grants, and the researchers' projects are successful. Thus, initiating grants for regulatory science will result in a potentially large increase in the likelihood of understanding all risks of FUS, depending on interest and quality of researchers.

#### *Facilitate Stakeholder Understanding of FDA Regulations*

Facilitating stakeholder understanding of FDA regulations would result in a medium increase in the likelihood of identifying risks. Fostering understanding that the goal, as far as FDA is concerned, is the development of special controls may facilitate more rigorous clinical trials, strategic thinking about future applications of FUS, development of innovative tools and tests, and willingness to share some information

with other companies facing the same challenges. These actions will all lead to greater understanding of the risks of FUS.

### ***Increase Direct-to-FDA Advocacy Efforts***

Increasing advocacy efforts with the FDA would cause a small increase in the likelihood of understanding all risks. Though advocacy does not directly facilitate understanding of risks, it may lead to a better identification of which risks are most salient to FDA. Having this information will make it easier to focus on aspects of FUS that concern the agency the most.

## **TIME REQUIRED**

### ***Maintain Current Funding and Support***

Maintaining current funding and support requires no implementation time. The lag time before FUS achieves Class II classification depends on the FUS Foundation's decision on the statutory alternatives.

### ***Offer Grants for FUS Regulatory Science***

Implementation of the grants offered for regulatory science through the NIH took roughly three years<sup>30</sup>. It took 7 months from posting the announcement for grant recipients to start their projects, and the grant period was 2 years. Assuming NIH took 5 months to prepare the announcement and funding means that a single grant took roughly 3 years to develop and administer.

Development of special controls is a direct requirement for reclassification, and this option directly addresses this requirement. If researchers are successful in developing methods to assess the risks of FUS devices, then FDA is more likely to be confident that the special controls will provide a reasonable assurance of safety and effectiveness. Thus, initiating grants for regulatory science will result in a potentially large increase in the likelihood of achieving classification in Class II.

### ***Facilitate Stakeholder Understanding of FDA Regulations***

Implementation of this option is likely to be concentrated at the Foundation's biennial symposium by hosting speakers and facilitating discussions. To ensure that stakeholders truly understand how FDA regulates medical devices, the FUS Foundation will need to host speakers at a minimum of two symposia. Between symposia the Foundation can host webinars or small discussions around FDA regulation. Including planning, this option will require a minimum of 2.5 years of concerted effort, though a positive reception from industry could warrant ongoing dialogue and education on the subject.

Facilitating this understanding, and hopefully collaboration, may cause a small decrease in lag time before FUS is classified in Class II. Industry awareness of FDA expectations, as well as a general understanding of FDA's process for reclassification, may lead to more comprehensive clinical trials and accelerate willingness to cooperate on a reclassification petition.

### ***Increase Direct-to-FDA Advocacy Efforts***

This option would involve ongoing efforts to forge connections with FDA. Therefore, there is no specific time for implementation, since these efforts could begin immediately and end immediately if the Foundation decided to focus on other areas.

Working directly with FDA could result in a medium decrease in lag time to achieving Class II. These efforts will increase FDA familiarity with FUS technologies, which may make them more receptive to new PMAs and later reclassification efforts. This relationship could also result in better understanding of FDA's current thinking on FUS classification so that the FUS Foundation or industry could act as soon as FDA indicates that it is open to the idea.

## **COST TO FUS FOUNDATION**

### ***Maintain Current Funding and Support***

Maintaining current funding and support would mean maintaining current allocation of the Foundation's roughly \$5 million operating budget.

### ***Offer Grants for FUS Regulatory Science***

Though the FUS Foundation could allocate as much or as little as they deem appropriate, the NIH grants for regulatory science ranged from \$200,000 to \$600,000<sup>30</sup>. The FUS Foundation could offer one grant in this range, then increase or decrease the number of grants and amount of funding in the future depending on success of the project and interest from researchers.

### ***Facilitate Stakeholder Understanding of FDA Regulations***

The primary cost for facilitating understanding of regulations would be compensation for speakers. It is likely that some speakers will donate their time, but regulatory consultants might charge the Foundation for their time, insight, and travel costs to reach a total cost of roughly \$5,000 over the course of the next 2.5 years.

### ***Increase Direct-to-FDA Advocacy Efforts***

Increases in direct-to-FDA advocacy could take multiple forms. Hiring consultants or lawyers to facilitate connections and provide strategy will cost at least \$5,000 a year. If the Foundation wants to substantially increase its regulatory affairs capacity it could hire a regulatory affairs specialist to facilitate this process. This specialist would likely require an average salary of \$55,000, not accounting for benefits, which is a rough estimate of an appropriate salary based on online job postings for similar positions.

# DECISION MATRIX

		Likelihood of Success		Time		Cost to FUS Foundation
		Understand All Risks	Achieve Class II	Implementation	Lag Time	
<b>Statutory Alternatives</b>	Wait for Industry Action	---	High	---	20 years	\$0
	Sponsor a <i>De Novo</i> Application	---	Low	100 hours	5-15 years	\$15K to \$70K
	Prepare and File a Petition for Reclassification	---	Very High	497 hours	15-20 years	\$75K to \$348K
<b>Other Options for Action*</b>	Maintain Current Funding and Support	Medium positive impact	---	---	---	~\$5 Mil
	Offer Grants for FUS Regulatory Science	Potentially large increase	---	3 years	Potentially large decrease	\$200K to \$600K
	Facilitate Stakeholder Understanding of FDA Regulations	Medium increase	---	2.5 years & ongoing	Small decrease	\$5K
	Increase Direct-to-FDA Advocacy Efforts	Small increase	---	Ongoing efforts	Medium decrease	\$5K - \$60K

\* Other options for action are assessed relative to the status quo, and characterized in terms of the magnitude of increases in likelihood of success.

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## RECOMMENDATION

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The FUS Foundation should wait for industry action for reclassification, and pursue all other options for action if possible. The Foundation should prioritize facilitation of stakeholder understanding of FDA regulations, and increase direct-to-FDA advocacy as stakeholders and the Foundation becomes more informed about the needs of the industry.

Waiting for industry action may increase the lag time for FUS to achieve Class II, but initiating a reclassification petition would be an extremely time and resource-intensive process for the Foundation. Thus, it would be more beneficial, for now, to focus on other options for action.

With this recommendation in mind, the FUS Foundation should work to facilitate stakeholder understanding of FDA regulations. Companies and other stakeholders have expressed frustration and confusion with the way FDA currently regulates FUS. Alleviating this frustration and confusion by providing opportunities to learn about FDA regulations and intentions will benefit stakeholders, and likely make industry more amenable to collaboration and strategic thinking around regulatory issues. Things like incorporating regulatory strategy into discussions about the future of FUS, hosting “FDA 101” seminars, and featuring knowledgeable speakers at the Symposium will help to initiate this understanding, and ensure the FUS community is well informed about regulatory challenges. This option could be used as a stepping-stone to other options such as an increase in direct-to-FDA advocacy, since a FUS community that is more engaged with regulatory issues is more likely to identify and articulate positive changes and strategies for advocacy. The Foundation should also, if possible, maintain current research funding levels while paying special attention to the possibility of offering special grants for regulatory science projects.

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## APPENDIX A: REGULATION OF SIMILAR DEVICES

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The Medical Device Amendments of 1976 established FDA's authority to regulate medical devices. Four device types that are similar to FUS were classified in the wake of the Medical Device Amendments: cryoablation, laser ablation, gamma knife (radionucleotide therapy), and radiofrequency ablation.

The Medical Device Amendments included provisions to classify medical devices into three risk-based classes, as well as requirements for general controls, performance standards, premarket notification, and premarket approval. Congress designed the 510(k) process as a way for medical device manufacturers with a device on the market before the Amendments to produce new variations on the "preamendment" devices. These manufacturers had to demonstrate that the new device was still "substantially equivalent" to the device already on the market before May 28<sup>th</sup>, 1976.

To serve as a reference for determining substantial equivalence, FDA created a list of preamendment devices. In 1972, the agency surveyed device manufacturers and solicited input from its classification panels to develop a list of devices that would require classification after passage of the Amendments. After the Amendments passed, the subject-matter-based classification panels sorted through the list of devices, divided the devices into regulatory categories, and classified each of these categories into Class I, II, or III.

Cryoablation was first documented in the medical literature in 1963, when Irving Cooper used liquid nitrogen for cryogenic freezing<sup>35</sup>. In 1978, FDA released a proposed rule to create Part 882 in Title 21 of the Code of Federal Regulations for neurological devices, and classify devices currently on the market (43 Fed. Reg., p. 55641). In this rule, FDA classified cryogenic systems for general neurological and spinal use into Class II, with a requirement for these manufacturers to demonstrate compliance with performance standards that would be determined in the future (43 Fed. Reg., p. 55680). In 1982, FDA released proposed rules for the General and Plastic Surgery Device Classification Panel, the Obstetrical and Gynecological Device Classification Panel, and the Gastroenterology and Urology Device Classification Panel's decisions on

cryosurgical devices used in each of their respective clinical areas (47 Fed. Reg., p. 2811). These panels recommended that cryosurgical units be classified into Class II with high-priority performance standards<sup>x</sup>, Class II with low-priority performance standards, and Class III with high priority premarket approval for liquid nitrogen devices respectively (47 Fed. Reg., p. 2830). Today, cryoablation systems fall under many different product codes depending on the device's intended use (GXH, NEJ, FAZ, and GEH), but all product codes refer back to the initial regulation, 882.4350.

FDA's General and Plastic Surgery Device Classification Panel classified laser ablation into Class II in 1982, based on the same list of preamendment devices it used to classify cryoablation systems (47 Fed. Reg., p. 2830). Laser ablation devices continue to fall under the regulation number 878.481 and product code GEX to this day.

Radiofrequency (RF) ablation devices, which use high frequency alternating current to ablate tissue, are currently generally regulated as Class II devices under regulation number 878.4400<sup>xi</sup>. FDA proposed the regulation number and Class II classification, which encompasses all "electrosurgical cutting and coagulation device[s] and accessories," (p. 2832) in 1982 based on the same list of preamendment devices as laser ablation and cryoablation (47 Fed. Reg., p. 2830).

Gamma knife, which uses gamma radiation to ablate tissue, is currently regulated under product code IWB ("System, Radiation Therapy, Radionucleotide") and regulation number 892.575 as a Class II device. This regulation number was proposed in 1982 by the Radiological Devices Panel when it classified devices from its 1972 preamendment devices list (47 Fed. Reg., p. 4408). This regulation encompasses all radionucleotide therapy systems, which the FDA defines as, "device[s] intended to permit the operator to administer gamma radiation therapy with the radiation source located at a distance from a

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<sup>x</sup> FDA notes the priority of developing performance standards in its later regulations because, as the number of classifications including performance standard increased, the burden on FDA to develop these standards increased. Thus, the agency denoted whether it should prioritize performance standards for some devices over others.

<sup>xi</sup> The majority of general RF ablation devices are represented by the product code GEI. Some specific indications of RF ablation, such as ablation of cardiac tissue, are represented in different product codes but are still Class II, and others, such as ablation for treatment of atrial fibrillation, are in Class III.

patient's body" (47 Fed. Reg., p. 4440). FDA classified radionucleotide therapy systems into Class II in 1982, with low-priority performance standards.

Over time, the understanding and definition of substantial equivalence has evolved to include devices beyond a single manufacturer or even a single technology. A predicate device or devices must have the same intended use and technological characteristics, or different technological characteristics that do not affect the device's risk profile, as the new device. Thus, many device sponsors conduct clinical trials or other tests to demonstrate that their device has the same technological characteristics as a predicate, and that the different technological characteristics do not change a device's risk to patients. For example, FDA cleared Intuitive Surgical's Da Vinci Surgical System in 2000 for general laparoscopic surgery under a Class II product code (NAY). Intuitive Surgical demonstrated that the robotic system is as safe and effective as standard laparoscopic surgery devices through clinical trials, which earned the system a ruling of "substantially equivalent" despite its highly innovative nature. Even RF ablation device companies still conduct clinical trials to support their 510(k) applications for new indications. Halt Medical presented results from a feasibility study, phase II longitudinal study, and phase III pivotal trial in their 510(k) application for use of RF ablation to treat uterine fibroids, which established substantial equivalence to Halt Medical's RF Ablation system indicated for soft tissue <sup>36</sup>.

FDA classifications were initially determined with little attention to specific indications for use since many classifications required input from multiple panels, yet only resulted in one regulation. Over time, however, FDA has become more sensitive to slight differences in indications, which has affected the way it classifies new devices and evaluates claims of substantial equivalence. For example, a new cryosurgical device for use in the uterus, HerOption, required premarket approval in 2001 under the MIK product code <sup>37373635</sup>.

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## **APPENDIX B: EXAMPLE OF SPECIAL CONTROLS**

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In 1976, FDA intended to create performance standards for class II devices. For example, FDA codified performance standards for light-emitting products, including lasers, in 1985 after its initial proposed classification of surgical lasers in 1982 (50 Fed. Reg. 33688). FDA and industry expressed concern that performance standards would take a long time to develop, and quickly become outdated. Thus, in 1990 this performance standard requirement changed into the idea of a special controls guidance document, which contains a list of all the risks of a device, treatment of a particular disease, or a combination of both, and identifies standards or tests to demonstrate mitigation of these risks. Many special controls find inspiration from standards created by the International Standards Organization (ISO), American National Standards Institute (ANSI), ASTM International<sup>xii</sup> (ASTM), or International Electrotechnical Commission (IEC). FDA designs these documents as recommendations for sponsors of 510(k) applications; it is careful to acknowledge that there are multiple ways to conduct testing, and the guidance document is simply a documentation of current FDA thinking on minimum requirements for demonstration of safety and effectiveness.

The March 2014 proposed rule intends to tie class II designation even more closely with special controls. Thus, it is likely that the FDA will be establishing more special controls documents to clear class II devices in the near future.

### **FOCUSED ULTRASOUND STIMULATOR SYSTEM FOR AESTHETIC USE**

FDA's *de novo* clearance process relies entirely on an ability to create a special controls document. In 2011, FDA cleared focused ultrasound for aesthetic use through the *de novo* process, and released a special controls guidance document<sup>33</sup>. This document contains a list of identified risks, as well as the measures it recommends to mitigate these risks (Table B.1). In the "Risks to Health" section of the guidance document, FDA writes:

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<sup>xii</sup> Known as the American Society for Testing and Materials until 2001

*In the table below, FDA has identified the risks to health generally associated with the use of the focused ultrasound stimulator system for aesthetic use addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as also shown in the table below. You should also conduct a risk analysis before submitting your premarket notification to identify any other risks specific to your device. We recommend the premarket notification describe the risk analysis method and include the results. If you elect to use an alternative approach to address a particular risk identified in this guidance document, or you have identified risks additional to those in the guidance, you should provide sufficient detail to support the approach you have used to address that risk<sup>33</sup>.*

<b>Table B.1: Special Controls for FUS for Aesthetic Use</b>	
<b>Identified Risk</b>	<b>Recommended Mitigation Measures</b>
Thermal Injury from Focused Ultrasound Exposure (Thermal Damage)	Section 6. Bench Testing Section 7. Software Validation Section 8. Animal Testing Section 9. Clinical Testing Section 11. Electromagnetic Compatibility Section 13. Labeling
Mechanical Injury from Focused Ultrasound Exposure (Cavitation or other Mechanical Damage)	Section 6. Bench Testing Section 7. Software Validation Section 8. Animal Testing Section 9. Clinical Testing Section 13. Labeling
Ocular Injury	Section 13. Labeling
Electrical Shock	Section 12. Electrical and Mechanical Safety Performance Testing Section 13. Labeling
Inflammation/Foreign Body Response	Section 10. Biocompatibility
Use Error	Section 13. Labeling

Each of the different sections provides general requirements for specific tests or labeling. Many of the performance testing requirements rely on international standards from the IEC and ISO. For example, FDA recommends that manufacturers demonstrate

electrical and mechanical safety using the standard “IEC 60601-2-37:2004-08 Particular requirements for the safety of ultrasonic medical diagnostic and monitoring equipment”

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## **LIST OF OTHER RELEVANT SPECIAL CONTROLS DOCUMENTS**

Development of special controls documents is a relatively new action. In the past, FDA issued guidances to help industry design clinical trials for particular devices, indication, or specific technical characteristics.

All of the *de novo* applications must be accompanied by a list of recommended special controls. Though FDA has not issued formal special controls guidance documents for many of the devices cleared through the process, it is possible to see the list of the devices cleared through the process, as well as summaries of proposed special controls on the FDA’s [De Novo Summaries page](#).

The FDA also released recent special controls documents in an effort to reclassify preamendment devices, such as the Class II Special Controls Guidance Document: Full Field Digital Mammography System ([March 27, 2012](#)) and Class II Special Controls Guidance Document: External Pacemaker Pulse Generator ([October 17 2011](#)).

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## **APPENDIX C: RECLASSIFICATION EXAMPLE**

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FDA estimates that it receives 6 reclassification petitions each year. These reclassification petitions can be initiated by FDA, though the agency generally only initiates reclassification for preamendment Class III 510(k) devices that it statutorily required to reclassify. For the past two years, FDA has focused on reclassifying the last of the Class III 510(k) devices rather than receiving petitions from industry for reclassification. Most of the time, industry groups or single companies file the petitions to be considered by the relevant classification panel. This appendix details a recent reclassification to demonstrate the type of information and preparation required for reclassification of a Class III device into Class II. Since FDASIA and the May 2014 proposed rule changed the reclassification process, there are few examples of the type of

reclassification that FUS would need to undergo before achieving Class II. The FDA posts all reclassifications from 2013 onwards on its [reclassification summary](#) page.

## **SHORTWAVE DIATHERMY FOR ALL OTHER USES**

Shortwave diathermy uses high frequency electrical current to stimulate tissue. Shortwave diathermy devices are preamendment devices; shortwave diathermy for generation of deep heat in tissues was classified into Class II, and shortwave diathermy for all other uses was classified into Class III following passage of the Amendments. Because these devices are preamendment, however, even the Class III indications required a 510(k) rather than a PMA. In an effort to complete classification of all Class III 510(k) device, FDA requested manufacturers of shortwave diathermy devices for uses other than therapeutic deep heat to provide evidence to assist the classification panel's decision. Ultimately, the panel proposed maintaining the Class III classification and required a PMA for all new non-thermal shortwave diathermy devices in July, 2012 (77 Fed. Reg., p. 39953). FDA received many comments from stakeholders on their proposed rule, many of which advocated for a Class II designation. Thus, in the wake of FDASIA, FDA initiated a public forum and convened a reclassification panel to reconsider the Class III requirement.

Four companies formed an industry coalition to show that all of the coalition devices fit FDA's definition of a Class II device <sup>25</sup>. These companies refuted FDA's claims about the risks of their technologies, and proposed special controls (Figure B.1) to address the realistic risks of their devices. They grounded their presentation in scientific literature, cited international standards and safety reports, and relied on a well-respected doctor and a current FDA staff member to deliver their arguments. At the end of the presentation, they presented a chart listing the risks and a summary of the types of special controls that could be used to mitigate these risks (Figure B.1).

Risk	IEEE C95.1	Electrical Safety	EMC	Preclinical Analysis	Labeling	Biocomp.	Clinical Information	QSR
Pacemaker Interference		✓	✓	✓	✓			✓
Tissue Necrosis and Burns	✓	✓		✓	✓		✓	✓
Wire Leads	✓	✓		✓	✓		✓	✓
Adverse Pregnancy Outcome	✓	✓			✓			✓
Risks to Children	✓	✓			✓			✓
Pain	✓				✓			✓
Skin Reaction	✓	✓			✓	✓		✓

**Figure B.1:** Shortwave Diathermy for All Other Uses Proposed Special Controls (Isenberg, 2013, p. 81)

Ultimately, the classification panel decided to classify the device in Class II. FDA writes, “there was panel consensus that although the effectiveness data were very limited, nonthermal SWD devices did not fit the regulatory definition of a class III device. Coupled with the rationale that special controls could be established to reasonably demonstrate an assurance of safety and effectiveness, the Panel recommended class II” (79 Fed. Reg., p.9670).

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## WORKS CITED

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1. *Federal Food, Drug, and Cosmetic Act. US Code* (1938).
2. FUS Foundation. Overview. *Focus. Ultrasound Found.* (2014). at <http://www.fusfoundation.org/the-foundation/foundation-overview>
3. Schlesinger, D. *et al.* MR-guided focused ultrasound surgery, present and future. *Med. Phys.* **40**, (2013).
4. Foley, J. L. *et al.* Image-guided focused ultrasound: state of the technology and the challenges that lie ahead. *Imaging Med.* **5**, 357–370 (2013).
5. *PMA P040003: FDA Summary of Safety and Effectiveness Data.* (2004). at <http://www.fda.gov/ohrms/dockets/dockets/05m0473/05m-0473-aav0001-03-ssed-vol1.pdf>
6. *PMA P110039: FDA Summary of Safety and Effectiveness Data.* (2012). at [http://www.accessdata.fda.gov/cdrh\\_docs/pdf11/P110039b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110039b.pdf)
7. FDA. *Draft Guidance; the 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications.* *Fed Reg Vol 76 No 249* (2009).
8. FDA. Regulatory Controls. *Med. Devices* (2013). at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/>
9. FDA. Classify Your Medical Device. *Med. Devices* (2012). at <http://www.fda.gov/20MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm>
10. FDA. Premarket Approval (PMA). *Med. Devices* (2012). at <http://www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.Htm>
11. U.S. Government Accountability Office. FDA Has Met Most Performance Goals but Device Reviews are Taking Longer. (2012). at <http://www.gao.gov/assets/590/588969.pdf>
12. FDA. *Proposed Rule: Medical Device Classification Procedures.* *Fed Reg Vol 79 No 57 16252–16265* (2014).

13. FDA. Ablation System, High Intensity Focused Ultrasound (Hifu), Mr-Guided. *Prod. Classif.* (2014). at  
<<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=4965>>
14. Tillman, D.-B. Approval Order: ExAblate 2000 System. (2004). at  
<[http://www.accessdata.fda.gov/cdrh\\_docs/pdf4/P040003a.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf4/P040003a.pdf)>
15. FDA. Recently-Approved Devices - ExAblate® 2000 System. (2004). at  
<<http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm080704.htm>>
16. Foreman, C. Approval Order: InSightec ExAblate® System, Model 2000/2100/2100 VI. (2012).
17. FDA. Summary of Safety and Effectiveness Data (ExAblate). (2012). at  
<[http://www.accessdata.fda.gov/cdrh\\_docs/pdf11/P110039b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110039b.pdf)>
18. FDA. Product Classification Database (Search:Ablation). *Med. Devices Databases* (2014). at  
<[http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?start\\_search=1&Submission\\_Type\\_ID=&DeviceName=ablation&ProductCode=&DeviceClass=&ThirdParty=&Panel=&RegulationNumber=&PAGENUM=25](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?start_search=1&Submission_Type_ID=&DeviceName=ablation&ProductCode=&DeviceClass=&ThirdParty=&Panel=&RegulationNumber=&PAGENUM=25)>
19. Monteris Medical. NeuroBlate System. (2013). at  
<<http://www.monteris.com/technology>>
20. FDA. Total Product Life Cycle (System, Radiation Therapy, Radionuclide). (2014). at  
<<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTPLC/tplc.cfm?id=4808>>
21. Visualase Inc. FDA Clearance – Visualase «. (2007). at  
<<http://www.visualaseinc.com/fda/>>
22. McGahan, J. P. & Raalte, V. A. van. in *Tumor Ablation* (eds. MD, E. vanSonnenberg, McMullen, W. N. & MD, L. S.) 3–16 (Springer New York, 2005). at  
<[http://link.springer.com/chapter/10.1007/0-387-28674-8\\_1](http://link.springer.com/chapter/10.1007/0-387-28674-8_1)>
23. FDA. How To Find A Predicate Device. *Device Advice* (2013). at  
<[http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134571.htm#link\\_3](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134571.htm#link_3)>

24. Levinson, D. FDA's Clearance of Medical Devices Through the 510(k) Process. (2013).
25. Isenberg, R. Reclassification of Nonthermal Shortwave Diathermy Devices: Industry Coalition Presentation. (2013). at  
<<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM359207.pdf>>
26. FDA. *Proposed rule: De Novo Classification Process (Evaluation of Automatic Class III Designation)*. 76 Fed Reg No 191 (2011).
27. FDA. Press Announcements - New FDA guidance on considerations used in device approval, de novo decisions. (2012). at  
<<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm297411.htm>>
28. FDA. Reclassification. (2014). at  
<<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm378724.htm>>
29. Sale, K. FDA Panel Recommends Class II Designation for Posterior Cervical Screw Fixation. *Am. Acad. Orthop. Surg.* (2013). at  
<<http://www.aaos.org/news/aaosnow/mar13/clinical8.asp>>
30. NIH. Funding Opportunities. *Off. Strateg. Coord.- Common Fund* (2011). at  
<<http://commonfund.nih.gov/regulatoryscience/grants>>
31. FDA. Research Project: Development and Use of Tissue Mimicking Materials (TMMs) for Assessment of HIFU Devices. (2012). at  
<<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm300578.htm>>
32. FDA. Research Project: Computational Techniques for Evaluating HIFU Safety and Effectiveness. (2012). at  
<<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm300579.htm>>
33. FDA. *Class II Special Controls Guidance Document: Focused Ultrasound Stimulator System for Aesthetic Use*. (2011).

34. *Medical Device Classification Procedures. 79 Fed Reg No 57 21 CFR Part 860* (2014).
35. Irving Cooper. Cryogenic Surgery — A New Method of Destruction or Extirpation of Benign or Malignant Tissues. *N. Engl. J. Med.* **268**, 743–749 (1963).
36. Halt Medical, Inc. 510(k) Summary: The Acesa System. (2012). at [http://www.accessdata.fda.gov/cdrh\\_docs/pdf12/K121858.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf12/K121858.pdf)
37. CryoGen, Inc. Summary of Safety and Effectiveness Data: Her Option™ Uterine Cryoblation Therapy™ System. (2001). at [http://www.accessdata.fda.gov/cdrh\\_docs/pdf/P000032b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/P000032b.pdf)