Regulatory Perspectives on Technologies for the Heart

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Note: The presentation on regulatory perspectives will be given by Sonna Patel-Raman of Halloran Consulting Group, Inc.

With advancements in material science, manufactures are able to develop medical devices[1] from stronger, superelastic materials and tissue, patient-specific or otherwise, opening the door for less-invasive surgical therapies and personalized medicine. Moreover, manufacturers have access to computers with substantial processing power, enabling them to use computational tools paired with patient-specific diagnostic images to simulate treatment options for patients, almost in real-time. In addition, with the increasing cost of health care alongside the aging baby boomer population, there is also a need to improve quality of life, decrease the number of doctor visits and length of hospital stays, and have more efficient treatment options that reduce cost for people living with heart disease, as highlighted in Table 1. The objectives of this paper are to highlight the regulatory process for medical devices from an engineering perspective, to discuss how manufactures of medical devices can leverage different tools and techniques to support putting their devices on the market, and how regulators might evaluate innovative medical technologies for the heart.

The Center for Devices and Radiological Health (CDRH) is responsible for regulating medical devices that are manufactured, repackaged, re-labeled, and/or imported to be sold in the U.S. Our mission "is to protect and promote the public health. We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S." [21]

The phrase "technologies for the heart" can refer to a myriad of cardiovascular devices that treat a range of diseases that affect the heart. A majority of the implantable devices to treat heart disease are

[1] A medical device is "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part, or accessory which is:

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes." [1]

classified as the highest risk, Class III, because they are life sustaining and/or life supporting. Some Class III implantable devices include pacemakers, defibrillators, heart valves, coronary stents, ventricular assist devices, and artificial hearts. Manufacturers that wish to market these devices in the U.S. need to demonstrate, based on valid scientific evidence, that there is a reasonable assurance of *safety* (that the probably benefits to health outweigh any probable risks) and *effectiveness* (that the device will provide clinically significant results). Comprehensive evaluation of a premarket submission for a therapeutic, high risk medical device is typically supported by a combination of valid scientific evidence from four types of models: animal, bench, computational and human. These models can be leveraged at different stages of life cycle of a medical device to demonstrate attributes of device performance. Because each model has different strengths and limitations for predicting real-world clinical outcomes, the data portfolio for different devices and use-conditions will vary. Some advantages of each model are highlighted in Table 2, and will be discussed in later sections.

Table 1. America's Heart Disease Burden

About 600,000 people die of heart disease in the United States every year–that's 1 in every 4 deaths [4]
Heart disease is the leading cause of death for both men and women. More than half of the deaths due to heart disease in 2009 were in men [4]
Coronary heart disease is the most common type of heart disease, killing nearly 380,000 people annually [4]
Every year about 720,000 Americans have a heart attack. Of these, 515,000 are a first heart attack and 205,000 happen in people who have already had a heart attack [5]
Coronary heart disease alone costs the United States $108.9 billion each year [6] This total includes the cost of health care services, medications, and lost productivity.

Table 2. Models and their Advantages

	Cost	Time	Ability to vary parameters	Evaluation involving harm	Simplifying assumptions	Relevance to Clinical Use	Evaluating disease state	Experimental control	Ability to interpret data and predict clinical use
Animal	moderate	moderate	limited	restricted	moderate	species variability	difficult	relatively high	limited
Bench	low	short	limited	yes	many and always	limited	simplified states	high	limited
Human	very high	long	not easy	no, unethical	minimal	direct	yes	low	not easy
Computer	relatively low	short - to - moderate	high	yes*	many and always	variable	yes*	high	yes*

Regulatory Evaluation

Selecting the appropriate model for evaluation

When a firm decides to manufacture a medical device, it is important that they consider the regulatory pathway that will allow that device to be marketed in the U.S. For many implantable devices to treat heart disease, a premarket approval (PMA) application is the appropriate pathway [7]. The firm also develops a plan to gather the necessary valid scientific evidence to demonstrate a reasonable assurance of safety and effectiveness. The basis of this plan will depend on the Indications for Use, i.e., the disease they intend to treat, the affected patient population, the location of the implanted device, the expected duration and *in vivo* conditions of the implant, and the surgical procedure. With this information, the firm can leverage tools such as the Device Evaluation Strategy [8] and the Failure Modes and Effects Analysis for Medical Devices [9]. These approaches serve to address fundamental questions about device failure and potential consequences (see Table 3).

Table 3. Questions from a FMEA

What is the device intended for?
What could go wrong?
Why would the failure happen?
What would be the consequences of failure?
What is the likelihood of occurrence?
What is the likelihood of detection?
What is the severity of the failure mode?

Depending on the function of the device, the firm would identify an attribute, the potential failure mode of that attribute, the potential device and clinical effect, the design characteristic intended to mitigate the risk of the failure mode, and the "model" that will be leveraged to demonstrate that the function of the device will be attained and/or that the failure mode will not likely occur. As previously mentioned, these "models" are animal, bench, computational, and human.

From the details in Table 2, it is clear that each model has unique advantages. For example, *in vivo* animal studies provide anatomic and clinical pathologic information of the local and systemic responses to device use. Larger animal models, such as pigs and sheep, are typically used for cardiovascular applications because the size and response of the anatomy more closely matches that of human anatomy. Bench and computational models can act as surrogates for the *in vivo* environment and

are useful because they can challenge an isolated feature of the device's attribute or function, e.g., implant integrity post-deployment, long-term durability. Clinical trials are used for a variety of purposes, but for Class III devices, they are mainly used to demonstrate safety and effectiveness in the clinical setting and evaluate the device in the *in vivo* human environment. Other applications of clinical evaluations can be found in FDA's guidance document "Investigational Device Exemptions for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human Studies" [8].

Unique Material Considerations

When a firm uses traditional materials, like stainless steel, and polyurethane, where the material behavior is well understood, then the regulatory expectations tend to be straight forward. However, when complex materials are introduced, and the material behaviors are not well established, additional engineering questions can arise. For example, there has been a shift from bare metal stents to drug eluting stents and more recently to absorbable stents. Some of the new questions for drug eluting stents focused on understanding the elution and absorption rates of the drug, in addition to the mechanical performance of the stent. With absorbable devices, one of the major concerns is the rate of degradation. Absorbable devices are not intended to be permanent implants like metallic stents, but they do need to maintain a certain amount of structural integrity. Firms leverage computational methods for stress analysis, but these methods can be challenging because the simulations require more complex constitutive models. Other challenges arise for both drug eluting and absorbable products when the manufacturing process changes because this can affect the elution and absorption rates for the drug or the degradation time frame for the absorbable material, which could result in additional testing. Identification of byproducts and their biological effect is a commonly recurring question as well, which can involve complex *in vivo* animal evaluations.

For tissue-engineered or regenerative medicine products that are medical devices, the regulatory framework is a bit different. Reviewers have to consider "purity, potency and identity" for biologically derived products [10], and this can pose limitations to traditional testing. For example, the long-term durability of permanent metallic implants, like stents and heart valve frames, can be evaluated using tools

like accelerated durability bench testing and computational modeling. These data complement the outcomes from the clinical study regarding mechanical performance. This is not the case for tissue and cell-based materials. Biologically dervied products are not generally tested in an accelerated fashion because the bench model does not allow for the cell and tissue adaptation process that occurs *in vivo* (e.g., cell infiltration and extracellular matrix deposition). Cell- and tissue-based products are dynamic systems, and that might enable the product to repair itself in a normal-timed setting *in vivo*; this cannot occur with accelerated bench testing. Therefore, manufacturers of biologic products must leverage significant *in vivo* animal testing for performance evaluation.

Changes to Surgical Approaches

As with a change in material, another aspect of device design that can affect regulatory questions is a change in surgical technique or approach. For example, there was recent introduction of a percutaneous approach for implanting heart valves for high risk patients; with that came a new set of questions regarding deliverability, deployment accuracy, integrity and migration. Integrity and durability are especially important questions because, before deployment, the device is loaded onto a delivery system and tracked through the cardiovascular system. This approach can impose new stresses and strains on the device in ways the traditional, open surgical approach does not – this is known as preconditioning. And, unlike surgical bioprosthetic heart valves, the transcatheter heart valves vary greatly in design; thus the effects of preconditioning can be different for each design. Moreover, unlike surgically implanted heart valves, the transcatheter heart valves do not usually remain circular upon implantation because the diseased leaflets and the calcium nodules are not removed; thus the frame experiences non-circular deformations *in vivo*. The computational model is the only tool that can be used to determine the changes in a stress (or strain) state of a device under different preconditioning states or implantation configurations. Furthermore, the computational model can predict how preconditioning and implantation [11] can affect fatigue performance. These predictions are then confirmed through accelerated durability testing.

In summary, firms provide valid scientific evidence from animal, bench, computational and human models to support their marketing applications, and the amount of data collected from each model depends on the disease they intend to treat, the affected patient population, the location of the implanted device, the expected duration of the implant, and the surgical procedure. As we move further into the 21st century, the data portfolio might change even more as firms expand their use of high performance scientific computing to reduce time and cost to bring safe and effective devices to patients in the U.S.

Treatment Planning in the 21st Century

The practice of medicine is being shaped by powerful imaging capabilities, high performance computation, wireless transmission of data, and massive storage of information. Physicians are now able to continuously monitor a patient's health from a distance; determine if a coronary lesion is relevant and if treatment is necessary, if a patient is at risk for losing heart rhythm, and if a patient will benefit from cardiac pacing [12]. Soon, physicians will be able to select the optimal heart valve size and placement and examine different treatment options, all within a matter of hours [13]. For example, Graphium Health, one of the companies in the Hive community [14], uses cloud computing and mobile technology to help physicians, administrators and patients make better pre- and post-surgery decisions about their care. HeartFlow, is using patient-specific anatomy and physiological conditions to computationally estimate the amount of coronary burden due to a stenosis; this alleviates the need for catheterization in moderate cases, which is an invasive procedure and currently the standard of care [15]. Because of these tremendous advancements, doctors have access to more data, information and knowledge, and the potential to offer more clinical benefit to their patients. However, regulators are challenged with trying to determine which of these advances in computing and software are medical devices, and if so, what data are needed to support their entrance to the market in the U.S. [16].

From an engineering perspective, scientific computing is mature enough to simulate multiple design parameters and use-conditions, and to visualize complex processes to revolutionize the way medical devices are investigated, treatments are planned, and patient data are utilized. With access to digital patients, device designers can download anatomic and physiologic computer models of patients

with a given disease [17, 18]. They can then take their new device concepts and "deploy" them in digital diseased patients and simulate device performance, leading to more effective bench testing, *in vivo* animal studies and (actual) clinical trials. The simulations will allow for the detection of "soft failures", failures that occur virtually before the devices are implanted in patients. Finally, from a clinical perspective, physicians will soon be able to use simulation to predict the safety and effectiveness of a given medical product for an individual patient, thereby being able to truly realize personalized medicine. However, the regulatory burden for medical devices that have the potential to predict patient-specific outcomes remains to be determined.

Conclusions

New materials and surgical approaches are generating more treatment options for patients with heart disease. Moreover, there is a huge opportunity for imaging and high performance computing to improve the net health outcomes of the U.S. population; with treatment planning and helping patients better understand their options. With the inception of efforts like the Health IT Initiative and the Hive, the potential has never been greater for the U.S. to better gather and leverage patient information and pertinent data relevant for efficient and optimal care. FDA's engagement with industry and academia early on in the development of innovative products can help accelerate the field. FDA can provide the structure to help guide firms to determine the appropriate models and data portfolio needs for evaluating their unique product. Also, engaging early enables FDA to share their regulatory experience and to raise the important questions that will protect patients and promote the overall health of the U.S population.

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