THE FDA'S 510(k) APPROVAL PROCESS AND THE SAFETY OF MEDICAL DEVICES

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ABSTRACT

Innovation fuels American business. Commonly, innovation is judged as *good*. Yet, many of the new medical devices that come on the U.S. market every year are later deemed unsafe. Regulation is distorted in that 98% of medical devices are never evaluated in human trials before being introduced to the marketplace. Instead, the U.S. Food and Drug Administration (FDA) approves a new medical device through a designated 501(k) process, based upon the identification of a predicate or substantially equivalent (SE) device. This is an investigation of the tension between product innovation, government regulation, and public safety in the American healthcare industry. It is a research project in two parts. The first draws upon established methodologies and utilizes the FDA's 501(k) database to provide an illustrated example of the sequence and dependency between generations of implanted surgical mesh devices. The analysis reveals that the 501(k) approval process reliance on predicate devices facilitates medical device innovation that is problematic in several aspects, including patient safety. To further examine medical device innovation and patient safety, the second study develops a proof-of-concept exercise to evaluate data on recorded adverse events (AEs) found in the FDA's Total Product Lifecyle (TPLC) database for surgical mesh products. The adverse events were mapped to the Association for the Advancement of Automotive Medicine's (AAAM's) Abbreviate Injury Scale (AIS), following precedents found in the medico-legal literature and military injury biomechanics standards. This approach forges a path forward to determine the relative frequency and severity of adverse events of a specific medical device, compared to that of the overall FDA product category. These two

research projects combine to contribute to the understanding of safety of the FDA's approval process and by extension the medical device industry's innovation practices.

Key words: Innovation, medical device industry, implanted device, substantially equivalent (SE), patient safety, U.S. Food and Drug Administration (FDA), 501(k) database, Total Product Lifecyle (TPLC) database, Association for the Advancement of Automotive Medicine (AAAM's) Abbreviated Injury Scale (AIS).

There is much work to be done.

Change is possible.

Tomorrow's progress is dependent upon today's advocacy.

For whom or what are you advocating?

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CHAPTER 1

INTRODUCTION

There are two blanket assumptions upon which the American marketplace for medical device manufacturing and distribution is sustained. They are: (1) Product innovation leads to better and safer products; and (2) federal government regulation via the Food and Drug Administration (FDA) protects patient safety. Evidence suggests neither of these is always true.

This research is an investigation of the tension between product innovation, government regulation, and patient safety in the American healthcare industry, specifically, that of innovation in medical devices. Medical devices are an essential component of healthcare, yet medical device approval occurs within a regulatory environment that is not widely understood. This spurs the first research objective of describing and evaluating the characteristics of the FDA's 510(k) approval process for medical devices. One substantial characteristic of this predominant approval process is the absence of an assessment of the patient safety of the devices. This leads naturally to a second area of inquiry, namely, the development and application of a process for assessing patient safety of medical devices approved through the 510(k) approval process. This two-part research approach highlights the tension involved in assuming that product innovation and existing government regulation are sufficient for protecting patient safety.

There are many complexities inherent in this research topic. To enable thoughtful reflection, a summary of the FDA regulatory process is provided in the next section. This is followed by an overview of the medical device sector, and an overview of the two-part research approach.

The FDA Process

In the United States, the Medical Device Amendments of 1976 put devices under the control the of the Food and Drug Administration (FDA). Industry's response was an impetuous one, claiming severe economic hardship, if it was going to be necessary to test all medical products that were already in use. The FDA agreed with the criticism from industry. The resolution was that anything on the market before 1976 was to be grandfathered, the FDA made no further testing demands of these 1976 and pre-1976 devices (Zeiring et al., 2018). This decision resulted in essentially two tracks: premarket approval (PMA) and 510(k).

> *Premarket Approval (PMA):* Premarket approval test devices for *safety and effectiveness* in at least one study with human subjects (FDA, 2019).

> *510(k):* The 510(k) process requires no human test subject activities as long as the new device is *substantially equivalent* to another device currently or formerly on the market (FDA, n.d.) Any substantial equivalence is identified on a company's application to the FDA as their (new) device's predicate.

Today, the percentage of all devices approved between these two processes is about 2% for PMA and 98% for 510(k) (Lenzer, 2017; Zeiring, 2018; FDA, 2019; MaxVal, 2019). (Table 1.) The overwhelming majority of devices are approved via 510(k) process, a result of *predicate creep,* as admitted by some industry experts (FDA, 2009, p.

2 – 3; GOA, 2009; Lenzer, 2017, p. 120). Essentially, a process suggested to manage an exception, at the inception of the 1976 legislation, is now the rule (Zeiring, 2018).

Table 1: Annual Medical Device Approval by FDA Process Type (2014 - 2018)

(FDA, 2019; MaxVal, 2019)

Year	Total Devices Approved	510(k) Approval Process		Premarket Approval Process	
		# of Devices by 510(k) Approval	% of Total Number of Devices	# of Devices by Premarket Approval	% of Total Number of Devices
2018	5,857	5,751	98.2%	106	1.8%
2017	5,925	5,827	98.4%	98	1.6%
2016	5,520	5,429	98.4%	91	1.6%
2015	5,193	5,107	98.4%	86	1.6%
2014	5,684	5,613	98.8%	71	1.2%

In 2011, the Institute of Medicine (IOM) conducted a review of FDA device approval processes. IOM's primary criticism was that the clearance process did not include an evaluation, either premarket or post-market, of the product's safety (IOM, 2011). In cases in which the product is truly a clone of a currently marketed device, substantial equivalency is not necessarily an incorrect standard (IOM, 2011). However, substantial equivalence does not guarantee that the device poses the same risks and performs similarly to an older device, particularly when the device is a chimera of multiple predicates (IOM, 2011). And the manufacturer can use as a predicate an old, discontinued device or a device that was approved, but never marketed (Committee on the Public Health Effectiveness of FDA's 510(k) Clearance Process, 2011). That same

year, Public Citizen concluded the 510(k) approval process favors the medical industry and puts consumers at risk (Wolfe, 2011). Essentially, most medical devices have never been tested for safety (Consumer Reports, 2012).

The Risk

The estimated human consequences of faulty processes and products are sobering. Allen (2013) reported that for 2007, medical interventions (including medical device implantation) were the third leading cause of death in the United States (behind heart disease and cancer), killing an estimated 210,000 to 440,000 Americans. In 2015, approximately 16,000 deaths associated with medical devices were reported to the FDA (Lenzer, 2017, p. 61).

An analysis from the General Accountability Office (GAO) found that 99% of device-related adverse events are never reported to the FDA, and the more serious the event, the less likely it is to be reported (Chelimsky, 1986). That means medical devices could have been associated with as many as 1.6 million deaths in 2015 (Lenzer, 2017, p. 61). Even if only 1% - 10% of those deaths were caused by a device, that means between 16,000 and 160,000 people may have been killed by devices, making medical devices [again] one of the leading causes of death in the United States (Lenzer, 2017, p. 61). Medical device industry is one of the most powerful yet unaccountable sectors of the medical-industrial complex (Lenzer, 2017, p. 67).

The Research

This research is an investigation of the tension between product innovation, government regulation, and public safety in the American healthcare industry, specifically, that of innovation in medical device manufacturing regulated by the United

States' Department of Health and Human Services, Food and Drug Administration (FDA). Succinctly, the research questions are two-fold:

1) What are the characteristics of the FDA's 510(k) approval process for medical devices, and how can the process be evaluated?
2) How can the relative patient safety of medical devices approved using the 510(k) process be assessed?

To answer these questions, the research is organized into two parts, the second building upon the first. The research begins in Chapter 2 with an exploration of the FDA's current and dominant 510(k) approval process, the *chain of innovation* precipitated by the identification of predicate devices, adopting methodology from Heneghan et al. (2017). Next, inspired by medico-legal precedence, a proof-of-concept exercise is developed in Chapter 3, with the intent being to compare patient safety concerns of a single device against the category of all surgical mesh devices. Patient safety data are collected for the FTL category of surgical mesh implanted devices, via entries in the FDA's Total Product Lifecyle (TPLC) database, and patient safety data are collected from the FDA's Manufacturer and User Facility Device Experience (MAUDE) database for the specific surgical mesh device, Ethicon's PROCEED Ventral Patch (PVP) Medium (6.5 cm x 6.5 cm) Mesh. The Association for the Advancement of Automotive Medicine's (AAAM's) Abbreviated Injury Scale (AIS) is applied to the patient safety data of the surgical mesh category as a whole, and to the patient safety data of the specific device. This approach for assessing the relative safety of medical devices holds potential for compelling practical application. By using recorded, defined and categorized adverse events (AEs), devices can be evaluated for their relative risk. More broadly, this offers insights into

whether the promise of medical device innovation, to improve or provide significant positive change in the life of a patient, is being fulfilled.

As detailed in the sections to follow, these complementary studies demonstrate that the 510(k) approval process is flawed and broken and reform is necessary and provide a way to bring attention to data on the relative patient safety of medical devices. The first study builds upon the work of Heneghan et al (2017). Heneghan et al. (2017) analyzed the 510(k) process for Boston Scientific's ProteGen Sling device, the original transvaginal mesh (TVM) device which is no longer in production along with all other TVM devices, due to overwhelming safety concerns. Their analysis revealed a daisy chain of innovation that was not focused on patient safety.

In our exercise, we reproduced Heneghan et al.'s (2017) study for a different product, an emerging surgical mesh product, TELA Bio's Ovine Tissue Matrix (OTM). The intent of the replication is to see if the sad case of TVM was a unique occurrence. If not, the sector could be just biding its time before another such FDA categorical device recall and cease production notice is issued. Results from the study documented a convoluted 510(k) approval process that crossed over decades of devices, suggesting that innovation and adaptation is not necessarily pursued or built upon the best device. The innovation model for medical devices is a crude whisper down the alley exercise with no documented concern for safety. Indeed, there was a duplication of two manufacturers (Cook Biotech and C.R. Bard) between our surgical mesh device tree and that of Heneghan et al. (2017). In addition, Cook Biotech self-referenced in the 510(k) sequence of devices for TELA Bio's Ovine Tissue Matrix and listed an older device of theirs as predicate for one of their new devices. This is very disconcerting because it suggests bad

devices can be unintentionally replicated in the daisy chain. This fact was underscored by the duplication of the Surgisis (Cook Biotech) brand name between Heneghan et al. (2017) study (for Boston Scientific's ProteGen Sling Collagen TVM) and ours (for TELA Bio's Ovine Tissue Matrix surgical mesh). Again, in summary, our research provides the necessary and verifiable evidence that the FDA 510(k) approval process is broken. Reform is needed.

However, before changes in the process can be agreed upon and made, research is needed to better understand the patient safety dimension. The second study contributes to understanding by applying the Association of the Advancement of Automotive Medicine's (AAAM's) Abbreviated Injury Scale (AIS) to assess the patient safety of implanted medical devices. This is a six-level scale of injury severity from Minor to Maximal. A seventh level is reserved for the Unknown. (Unknown examples include pain, insufficient information and depression.) The AIS scale was applied to the FDA's patient safety data for the overall FTL category of surgical mesh and to an individual surgical mesh device, Ethicon's PROCEED Ventral Patch (PVP) Medium (6.5 cm x 6.5 cm). FDA data sources were Total Product Life Cycle (TPLC) and Manufacturers and User Facility Device Experience (MAUDE), respectively.

In the comparison of the specific surgical mesh product, Ethicon's PROCEED Ventral Patch (PVP) Medium (6.5 cm x 6.5 cm) Mesh, to the entire FTL category of devices, it appears the individual Ethicon PVP Medium Mesh devices performs better along both quantity and quality dimensions. Regarding quantity, over the two years of data considered, while there were 100 different patient problems reported for FTL product category, there were 35 types of patient problems for Ethicon PVP Medium

mesh. In addition, perhaps more significantly, there were no recorded deaths for Ethicon's PVP Medium Mesh, while there were 14 deaths in the full FTL category of mesh devices. Regarding quality, over the same two years of data considered, there were proportionately fewer problems with greater severity for Ethicon's PVP Medium Mesh in comparison to FTL product category of all mesh devices. Specifically, in the data reported, 28% of patient problem in FTL product category are 3/Serious, 4/Severe, 5/Critical, or 6/Maximal. In contrast, only approximately 14% of patient problems for Ethicon's PVP Medium Mesh are scaled as 3/Serious, 4/Severe, 5/Critical or 6/Maximal.

This application was an effective proof of concept. The proof-of-concept exercise demonstrated feasibility in this approach to comparing the safety of medical devices. It holds promise for distinguishing the relative patient safety of implanted medical devices. This proof of concept can contribute to current and future efforts to highlight patient safety in the medical device approval process.

Taken together, the contribution of these two complementary studies is demonstrable evidence that although the 510(k) process is broken, there is a feasible and useful way to bring into the process a measure of patient safety. Applying the Association for the Advancement of Automotive Medicine's (AAAM's) Abbreviated Injury Scale (AIS) to FDA information available in the Total Product Life Cycle (TPLC) and Manufacturer and User Facility Device Experience (MAUDE) database can evaluate the relative and comparative safety of medical devices. Details of these two studies are provided in the subsequent three chapters and are followed by a final chapter with conclusions and insights.

CHAPTER 2

INSIGHTS FROM A MEDICAL DEVICE CHAIN OF INNOVATION TRACED THROUGH THE FDA'S 510(k) DATABASE

Introduction

Innovation fuels American business. Commonly, innovation is judged as *good*. Regulation is a critical component of the business environment. The idea is that private industry manufacturers, metered by federal regulatory bodies, should be introducing the best products to the marketplace. For consumers, safety is an extension of the value proposition of the *best* product. Exploring this intersection of innovation, regulation, and patient safety is especially relevant in the context of medical devices. The complexity of the medical device business environment leads to the first research question: What are the characteristics of the FDA's 510(k) approval process for medical devices?

The first study seeks an answer to this question by creating the family tree of a medical device based upon methodology originally exercised by Heneghan et al. (2017). While Heneghan et al, had a point of origin being Boston Scientific's ProteGen Sling device, our point of origin is TELA Bio's Ovine Tissue Matrix (OTM), which is a more recent surgical device introduced to the market. While anecdotally, many say the 510(k) process is broken, this study aims to show how and where the problems lie. It has previously been established that there is not a linear progression of device innovation, as the process is convoluted and refers back to manufacturers and products with safety risks. This study demonstrates two nefarious realities, one being this kind of whisper down the alley sequence of device innovation, and the other being that a faulted or outright broken device could most certainly infiltrate the daisy chain and easily become a reference point

for a future device. These findings imply that the regulatory process has the potential to perpetuate risk to patient safety.

The study is presented as follows. The first step is to lay the foundation with the broader context with respect to innovation, regulation and industry. To place our contribution within the business environment, a research scaffold is shared (see Figure 1). For the ground level, the healthcare industry as an economic force will be established. Next within this industry, we zero in upon medical devices found within the surgical appliances and supplies segment of the sector of medical equipment manufacturers (of the U.S. healthcare market). The literature review focuses on two primary themes. The first theme is the topic of innovation, its theories, and ascribed *value* rounded-out with specific research on this topic as it relates to the medical device industry. The second theme is the role of regulation in corporate innovation. This is a critical component because the process of medical device innovation in the United States is dominated by the 510(k) approval process. This information is assimilated in a review of the success of regulatory management in three specific industries: automobile manufacturing, audio and video equipment manufacturing, and pharmaceutical preparation manufacturing. The necessity and inference of safety for the consumer will be discussed.

Lastly, the review looks at the FDA's recall and cease distribution and notification process and its categorical application in the case of Boston Scientific's ProteGen Sling. This will springboard us to the original academic contribution, inspired by Heneghan et al (2017)'s analysis of the device chain approval for transvaginal mesh. The primary source for the work is the FDA's 510(k) Premarket Notification public database.

The Economics – United States Healthcare

United States healthcare is big business. From 1960 to 2019, healthcare expenditures as a percentage of U.S. gross domestic product (GDP) increased from 5% to 17.8% (Statistica, n.d.) (Figure 2.) In 2019, this percentage (17.8%) represented approximately $3.8 trillion (Statistica, n.d.) This makes healthcare the fifth largest American industry behind (1) real estate, (2) professional and business services, (3) state and local governments and (4) finance and insurance (Levin, 2019).

According to the Centers for Medicare and Medicaid Services (CMS) (n.d.), national health spending is expected to grow at an average rate of 5.5% per year between now and 2027, when it is projected to reach nearly $6.0 trillion. On the employment front, the U.S. Bureau of Labor and Statistics predicts 14% growth in healthcare occupations (or 1.9 million new jobs) between 2018 and 2028. This is much faster than the average for other occupations (U.S. Bureau of Labor and Statistics, n.d.). Investopedia reports healthcare is the number one industry driving the U.S. economy since 2008, followed by technology, retail, construction, and non-durable manufacturing (Deutsch, 2019).

There are four sectors of the U.S. healthcare market: drug manufacturers, medical equipment makers, managed healthcare, and healthcare facilities (Chappelow, 2019). Medical technology producers, commonly referred to as medical device manufacturers, are counted within medical equipment makers. Medical technology is complex (as summarized in Table 2), and ranges across articles, instruments, apparatuses, or machines that are used in the prevention, diagnosis or treatment of illnesses or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the

body for some health purposes (U.S. Department of Commerce, n.d.). Typically, the purpose of a medical device is not achieved by pharmacological, immunological, or metabolic means (U.S. Department of Commerce, n.d.)

Table 2: Definition of Critical Terms

(Various)

Term	Definition	Source
Medical Technology	Medical technology consists of articles, instruments, apparatuses, or machines that are used in the prevention, diagnosis or treatment of illnesses or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some health purposes. Typically, the purpose of a medical device is not achieved by pharmacological, immunological, or metabolic means.	U.S Department of Commerce, n.d.
Innovation	A good or service that is new or significantly improved. This includes significant improvements in technical specifications, components and materials, software in the product, user friendliness or other functional characteristics.	U.S. Organization for Economic Cooperation and Development (OECD), n.d.
Regulation	Imposition of rules by government, backed by the use of penalties, that are intended specifically to modify the economic behavior of individual firms in the private sector.	U.S. Organization for Economic Cooperation and Development (OECD), n.d.
Medical Device Recall	When a manufacturer takes a correction or removal action to address a problem with a medical device that violates FDA law. Recalls occur when a medical device is defective, when it could be a risk to health,	U.S. Food & Drug Administration (FDA), 2018

	or when it is both defective and a risk to health.	
Cease Distribution and Notification Order	When issued, FDA requests reasonable efforts to ensure and verify all health professionals, device user facilities, consignees and individuals have been notified on the order and have been instructed to cease use of the device or take other appropriate action, so the use of the device will not cause serious, adverse health consequences or death.	U.S Food & Drug Administration (FDA), 2019
Implantable Devices	A category of medical devices that are inserted into the human body to replace a missing body part, support a damaged body part, or modify an important body function. Examples of implantable devices include orthopedic rods, pins, and screws used to repair fractured bones; artificial hip joints used to replace hip bones worn by arthritis; and cardiac pacemakers used to restore an irregular heart rhythm.	Lind, 2017
Foreign Body Reaction (FBR)	Inflammatory response proved by implanted materials such as medical devices.	Luttikhuizen et al., 2006
510(k) Premarket Submission & Predicate	Filing of the 510(k) form is a premarket submission made to the FDA to demonstrate that the device to be marketed is safe and effective, that is, substantially equivalent (SE) to a legally marketed device. The legally marketed device(s) to which the equivalence is drawn is commonly known as the predicate.	U.S Food & Drug Administration (FDA), 2020
Substantially Equivalent (SE)	A device is substantially equivalent if, in comparison to the predict it:	U.S. Food & Drug Administration (FDA), 2020

	• Has the same intended use as the predicate and • Has the same technological characteristics as the predicate; or • Has the same intended use as the predicate; and • Has different technological characteristics and does not raise different questions of safety and effectiveness; and The information submitted to FDA demonstrates that the device is as safe and effective as the legally marketed device.	
Predicate Creep	First described by the U.S. General Accountability Office in January 2009, a result of 510(k) process, is that a *submission for a new device in 2008 could be compared to the 20th iteration of a device type that was on the market before 1976.* Then, as reported by the FDA in September 2009, *predicate creep* is mentioned as a phenomenon peculiar to the 510(k) program. Documented *as minor differences among successive device predicates accumulate so that even if a device and its immediate predicate are similar, the last cleared predicate and the generic type of device described in the classification regulation can be made from different materials, use different power sources, and have indications for different anatomical sites.* Following, the term becomes a colloquialism and is adopted industry-wide and beyond.	U.S Food and Drug Administration (FDA), 2009 and U.S. General Accountability Office (GAO), 2009

The Economics – United States Medical Technology Industry

The global medical device market was valued at $425.5 billion in 2018 (Fortune Business Insights, 2019). The United States is the largest national medical device market in the world (U.S. Department of Commerce, n.d.), as shown in Figure 3. In 2017, the U.S. medical technology and device industry generated $156 billion in revenue (U.S. Department of Commerce, n.d.) This number is expected to reach $208 billion by 2023 (U.S. Department of Commerce, n.d.) There are six subsectors or segments of the medical device industry according to U.S. Department of Commerce (n.d.): dental equipment and supplies, electro-medical equipment, in-vitro diagnostics, irradiation apparatuses, surgical and medical instruments, and surgical appliances and supplies (see Table 3 and Figure 4). Over the past ten years, an estimated 70 million Americans have been implanted with medical devices (Lenzer, 2017, p. 60). Within that population, the American Association of Retired Persons (AARP) reports 370,000 pacemakers are implanted and one million hip and knee replacements are performed annually (Lind, 2017).

Table 3: Medical Technology Industry Subsectors

(U.S. Department of Commerce, n.d.)

Subsector	Description
Dental Equipment and Supplies	Includes equipment, instruments, and supplies used by dentists, dental hygienists and laboratories. Specific products include dental hand instruments, plaster, drills, amalgams, cements, sterilizers and dental chairs.
Electro-medical Equipment	Includes a variety of powered devices, such as pacemakers, patient-monitoring systems, MRI machines, diagnostic imaging equipment (including informatics equipment) and ultrasonic scanning devices.
In-Vitro Diagnostics	Includes chemical, biological or radioactive substances used for diagnostic tests performed in test tubes, Petri dishes, machines and other diagnostic test-type devices.
Irradiation Apparatuses	Includes X-rays devices and other diagnostic imaging, as well as, computed tomography equipment.
Surgical and Medical Instruments	Includes anesthesia apparatuses, orthopedic instruments, optical diagnostic apparatuses, blood transfusion devices, syringes, hypodermic needles and catheters.
Surgical Appliances and Supplies	Includes artificial joints and limbs, stents, orthopedic appliances, surgical dressings, disposable surgical drapes, hydrotherapy appliances, surgical kits, rubber medical and surgical gloves and wheelchairs.

Implantable devices are defined as (see Table 2) a category of medical devices that are inserted into the human body to replace a missing body part, support a damaged body part, or modify an important body function (Lind, 2017). Examples of implantable devices include orthopedic rods, pins, and screws used to repair fractured bones; artificial hip joints used to replace hip bones worn by arthritis; and cardiac pacemakers used to restore an irregular heart rhythm (Lind, 2017). Prospectively, one in ten Americans will have a medical device implanted over their lifetime (Ziering et al., 2018). This translates into a per capita expenditure of $399, the highest in the world (Harrington, 2015).

Medical devices are a way of life in American healthcare, an assumption of post-industrial society and, in some ways, an indication of the potential of modern medicine,

as an enabler of longer and better-quality lives (Ziering et al., 2018). With this economic structure and impact understood, we can turn our attention to the academic theories of innovation, its value, and particularly its application within the medical device industry.

Literature Review

Following our research scaffolding, this literature review explores the topics of innovation and regulation (see Figure 1 and Table 2). Specifically, we first examine the general theories related to innovation and its associated value. Then, we examine the role of regulation within the business environment using specific industry examples (automobile manufacturing, audio and video equipment manufacturing and pharmaceutical preparation manufacturing). Finally, we will consider completed research on safety and regulation within the medical device industry.

Theories of Innovation

The only constant is change. Medical technology companies, like all businesses, respond to their environment seeking to leverage their corporate knowledge to solve problems and address market demands and consumer needs. Such responses are born from an innovation process of some sorts. A sampling of key innovation concepts or theories found in management literature are identified in Table 4 below.

Table 4: Innovation Theory Names, Description & Examples

(Various)

Theory	Description (Sources)	Example
Creative Destruction	A classic theory, it is the process of industrial mutation that incessantly revolutionizes the economic structure from within, incessantly destroying the old one, incessantly creating a new one (Schumpeter, 1942). As Naqshbandi and Kaur (2015, p. 42) simplify: Creative destruction takes place when something new replaces something older.	Ford Company's installation of a moving assembly line for mass production in 1923.
Incremental Innovation	Products [or services] created as a result of knowledge that builds on the existing knowledge of a firm, therefore this form of innovation is competence-enhancing (Naqshbandi and Kaur, 2015, p. 43).	Coca-Cola's introduction of Cherry Coke to the mainstream market in 1985.
Radical Innovation	It stands in contrast to incremental innovation. As Naqshbandi and Kaur (2015, p. 43) summarize: The technological knowledge required to exploit radical innovation is different from existing knowledge, the existing knowledge becomes obsolete. They continue and stipulate radical innovation thus requires new knowledge or resources and is competence-destroying (Naqshbandi and Kaur, 2015, p. 43).	Arrival of Blu-ray Disc in in 2006 that forever supplanted high-definition digital video disks (HD DVD) and video-cassette recording (VCR) tapes.
Disruptive Innovation	Innovations that help create new markets and value networks (Christenson, 1997).	Streaming video services launched by Netflix in 2007.
Open Innovation	When firms use external ideas as well as internal ideas and internal and external paths to market (Naqshbandi & Kaur, 2015, p. 46) The use of purposive inflows and outflows of knowledge to accelerate internal innovation and expand the markets for external use of innovation (Chesbrough, 2003).	Proctor & Gamble's (P&G's) crowdsourcing strategies that resulted in the introduction of Swiffer Dusters in 2003.

Closed Innovation	When the internal research and development function of traditional, vertically integrated businesses leads to products conceived and built internally and distributed thereafter (Naqshbandi and Kaur, 2015, p. 46).	First commercial order taken for GORE-TEX fabric received in 1976, seven years after original discovery of the expandable properties of polytetrafluoroethylene by W.L. Gore & Associates, Inc.
Modular Innovation	Products are composed of components or modules and the links between them are referred to as their architecture. In modular innovation, knowledge of one or more components is required to make a major change; but only a minor change in architecture is made (Henderson & Clark, 1990).	The change from analog to digital telephony which started in the 1960s.
Architectural Innovation	In contrast to modular innovation, here, established systems are reconfigured to link existing components in new ways (Naqshbandi and Kaur, 2015, p. 45).	Sony's introduction of the Walkman in 1979.

Although this is not an exhaustive list, it is a representative one of popular theories and concepts of innovation.

The Implied Value of Innovation

Regardless of the type of innovation employed, there is an implied benefit of its outcome or results. The United States' Organization for Economic Cooperation and Development (OECD) (n.d.) defines product innovation as a good or service that is new or significantly improved. This includes improvements in technical specifications, components or materials, software in products, user-friendliness or other functional characteristics (OECD, n.d.). (Table 2.) Berkun (2010, p. XVII) simply states that innovation is significant positive change. Schumpeter (1942) recognizes the potential for innovation to catapult a firm to monopolistic status. The dynamism of radical innovation results in products that involve large technological advancements and are superior to

existing products (Naqshbandi & Kaur, 2015, p. 43). In the case of incremental innovation, companies remain in a better position by leveraging the existing knowledge of their resources.

Chesbrough (2003) says firms throughout the 20th century profited from innovations that were the outcomes of substantial investments in research and development. He continues by distinguishing between open and closed innovation. In a closed innovation model, firms will win if the most and best deals in the industry are created by them. In an open innovation model, internal and external ideas are necessary to win, and a firm can benefit from their own intellectual property (IP), while also benefiting from the intellectual property of other individuals or entities (Chesbrough, 2003). In comparison, disruptive innovation takes place as a process; product enhancements result in improved product performance (Naqshbandi & Kaur, 2015, p. 47).

Regardless of the innovation method, the literature seems to suggest that the quality of the consumer experience is improved by adopting the new innovative products and services, but the process to achieve that value is not always clear. Another suggestion is that there may be dimensions of innovation depending upon one's perspective: consumer benefits, user safety, marketplace negotiations or company efficiency, e.g. This is begging the question of whom is benefiting from what innovation(s)?

The Role of Regulation

In most industries, regulatory bodies play a major role in new products and services to the market. The OECD (n.d.) defines regulation as the imposition of a rule by government, backed by use of penalties intended specifically to modify the economic

behavior of individuals and firms in the private sector (Table 2). In a global context, cross-border regulation aims to define acceptable and legitimate business behavior (Djelic & Quack, 2018, p. 124). In a national forum, regulation is often viewed as an affront to the economic value of free markets. In response to this, Etzioni (2009, p. 40) candidly editorializes: To regulate or not is not a question, because there never was a free market. He continues saying markets have always been managed, in some context, throughout economic history (Etzioni, 2009, p. 40). Essentially, there are no free markets; only different levels or kinds of regulations (Etzioni, 2009, p. 46).

Regulations are not merely for ensuring basic human needs that could be wantonly denied by agents seeking to maximize profit. Regulations also secure and protect business e.g., safeguard trade secrets; define markets by zoning and provide insulation from *cutthroat* competition (Etzioni, 2009, p. 41). Shaffer (1995) argues that the effects of government [regulation] on competitive position are important determinant of profitability. Norman (2011) posits that a corporation's practice in the following (or not) of government regulation is an ethical issue. He urges companies to think about their obligations beyond just compliance to existing regulations, as regulations reflect minimum standards (Norman, 2011). Studying Europe, Barbosa and Faria (2011) report regulators impact innovation activity by changing the level of competition or affecting the allocation of resources. They find innovation can be encouraged by regulation that provides access to credit markets, but their work is inconclusive as to whether strengthening intellectual property rights stimulates innovation.

Corporate innovation can be facilitated by laws that encourage training, as trained employees seem to be more successful in their motivation, productivity, and innovative

pursuits (Acharya et al., 2010). More competition in an industry between neck-and neck players begets more innovation, so Aghion et al. (2005) argue for regulation that welcomes competitors. In summary, regulation is an inescapable part of the business environment and regulatory processes impact innovation activity.

Examples of Industry Innovation Providing Value Guided by Federal Regulation

Now we will consider the ability of three industries, working with their federal regulatory partners, to deliver on the benefits of innovation.

Automobile Manufacturing (NAICS 336111): In the United States, automobile manufacturing and safety are regulated by the Department of Transportation's (DOT's) National Highway Traffic and Safety Administration (NHTSA). The NHTSA's stated mission is to save lives, prevent injuries and reduce vehicle-related crashes (DOT, n.d.) (Figure 5.)

The DOT's NHTSA (n.d.) reminds us that newer cars are safer cars. This is because of recent innovations in equipment and technology like seat belts, air bags, electronic stability control, backup camera, blind spot detection and driver assistance to name a few (DOT, n.d.) (Choksey, 2013). Analysis of NHTSA's crash data suggests the average vehicle on the road in 2012 has an estimated 56% lower fatality risk for its occupants than the average vehicle on the road in the late 1950s. The U.S. population has been growing steadily since 1975, while the rate of crash deaths per 100,000 population in 2018 is about half of what it was four decades ago. (Figure 5.) From 2017 to 2018, the per capita death rate from

crashes decreased three percent, even with 65 million more vehicles in the United States than there are drivers (DOT, n.d.). In this way, the promise of innovation seems to be fulfilled through the cooperation of the United States auto manufacturers and the DOT.

Audio and Video Equipment Manufacturing (NAICS 334310): Specifically, we will look at the manufacturing of televisions sets. One of the regulatory bodies overseeing this industry is the Consumer Product Safety Commission (CPSC). (Table 4.) Examples of some of the CPSC's (n.d.) codes for this industry are electronic cord maintenance, fire and burn prevention, electrical shock prevention, antenna maintenance and handling, exposure to liquids and tip-over avoidance. Despite the constant presence of the CPSC, innovation in television picture quality persists. The first commercial television was available in 1925. Through the decades, images were broadcast in black and white, then color, offered manual remote control, now voice-activated control and progressed from standard-definition to high-definition images to ultra-high definition (4K and beyond). Picture quality is driven by the number of horizontal lines that a television can show, expressed by the number of pixels (Finlux, n.d.) For instance, a 720p high-def (HD) ready television projects 720 lines across its screen (Finlux, n.d.) Innovations in semiconductor engineering have brought us 8K (Shalinsky, 2010). (Figure 6.) This all within the last twelve years, as United States transitioned from analog to digital television in 2010 (Shalinsky, 2015). Ultra-high-definition television supports 60 frames per second, similar to 35-millimeter film and twice

that of standard-definition (TechTarget, 2008) Today's screens utilize a greater aspect ratio, based upon research showing the viewer's experience is enhanced by wider screens (TechTarget, 2008.) These strides, along with improvements in audio quality which supports Dolby Digital 5.1 outputs, brings the theatre experience home (TechTarget, 2008.) In summary, Americans have enjoyed steadily increasing quality television viewing, regulated by the CPSC, all from the security and comfort of their living rooms.

Pharmaceutical Preparation Manufacturing (NAICS 325412): American Cancer Society (2020) estimates 1.8 million new cancer diagnoses in 2020; 15% of those will be breast cancer ones. Within healthcare, from 1975 to 2010, advancements in treatments of breast cancer have reduced mortality rates by 32% (Narod et al., 2015). In addition, between 1975 – 2002, the ten-year survival rate for regional breast cancer patients increased by 28% (from 64.9% to 82.8%) (Narod et al., 2015). Technological improvements in screening and diagnostics, advanced radiation therapies, genetic knowledge, immunotherapy, nanotechnology, better chemotherapy and pharmacological offerings are some of healthcare innovations credited with this impact (Cleveland Clinic, n.d.) (Charmsaz et al., 2018.) Women under the age of 50 have seen a particularly strong decline in death rates due to breast cancer because of improved screening and treatment of the disease (Healthline, n.d.) The adoption of innovative chemotherapies demonstrates a clear impact upon breast cancer patient fatality statistics (Narod et al., 2015). (Figure 7.) Those cited include Cyclophosphamide, Methotrexate, Fluorouracil (CMF),

Tamoxifen, Anthracyclines, Taxanes, Herceptin, and Aromatase Inhibitors (Ais) (Narod et al., 2015).

The introduction of such pharmacological regiments is regulated by the FDA. (Table 4.) The FDA (2019) evaluates new drugs before they can be sold. This prevents quackery and provides doctors and patients the information they need to use medicines wisely. The FDA ensures that drugs, both brand name and generic, work correctly and their health benefits outweigh their known risks. For chemotherapies, clinical trial data is required that scientifically documents efficacy, expected benefits, toxicities, prognosis of therapy for patients, among other details (Crean & Jones, n.d.) (Sipp et al., 2017). The innovation process in the pharmaceutical industry has increased the quality and duration of life expectancy for breast cancer patients, while adhering to federal regulations.

While the promise and benefit of innovation in the manufacturing of automobiles, television sets and pharmaceuticals (for the treatment of breast cancer) for consumers remains intact and is facilitated by their federal regulatory partners, is this true for the medical technology industry?

Innovation within the Medical Device Industry

For many, the recognized academic stalwarts on creativity and innovation are Amabile and Pratt. Amabile and Pratt (2016) argue that creativity and innovation are different parts of the same process within an organization. Specifically, they state that creativity is the production of novel and useful ideas by an individual or small group of

individuals working together, ambiguously described as *the fuzzy front-end* of innovation, while innovation is the successful implementation of creative ideas within an organization. Both creativity and innovation are socially bound by time and place, meaning what is novel in a domain is a function of what already exists in that domain (Amabile & Pratt, 2016).

Russell and Tippett (2015, p. 36) investigate this fuzzy-front end in the medical device industry and identified 16 critical success factors, which they organized into one of three categories. Those were:

(1) *developing a business case prior to project approval*

(2) *producing a new product development strategy for the innovation team and*

(3) *promoting a culture of innovation*.

Interestingly, development of new medical devices generally takes place in small entrepreneurial companies and once an introduction is made, larger corporations tend to buy smaller companies and their products (Gelijns & Halm, 1991). One of the primary reasons we see this is that regulatory and product risk restraints are not nearly as strong for medical device firms, in comparison, say, to the pharmaceutical drug industry (Gelijns & Halm, 1991). Drugs must undergo two clinical trials (with human subjects), before hitting the market, but fewer than half a percent of high-risk medical devices have undergone that standard (Young, 2018). Of the high-risk devices that have, only five percent underwent two clinical trials, and those clinical trials were not necessarily trustworthy (Young, 2018). These clinical trials are often small (50-100 people) and conducted over a short amount of time (Ziering et al., 2018).

Another reason for this pattern of innovation, is that the market for new devices is often ill-defined (Gelijns & Halm, 1991). Chatterji (2008) finds that new medical device ventures spawned by former employees of incumbent medical device firms perform better than other new entrants. It is not only these employee's technical knowledge per se that forges their firm's paths to success, it also includes their knowledge related to regulatory issues and marketing. So, innovation theory goes out the window? For the emerging medical device firm, it seems to be all about FDA approval and sales.

Innovation in medical technology is a critical chain of events, ideally leading to an improved situation for patient and staff, as well as a profit for the supplier of the innovation (Wieringa et al., 2007). But outcomes are not always encouraging. Many believe medical technology innovation and regulatory processes are flawed. Simply, a majority of promising medical device innovations are not effective in practice (Wieringa et al., 2007) (Shobeiri, 2019). Some are harsher and report there is a theme of abuse of innovation in the medical device industry (Ziering et al., 2018). Assessing the recent launch of Intuitive's robotic-assisted surgical device called the da Vinci, Dr. Martin Makary, Professor of Surgery and Health Policy John Hopkins School of Medicine, ominously concluded that there seems to be a massive adoption of technology with little or no concern for outcomes (Ziering et al., 2018). In the current system, physicians are gatekeepers for new-product implementation (Wizemann, 2010). Decisions need to be evidence-based, but the line between when there is enough data to allow a product onto the market and physician responsibility is not clear (Wizemann, 2010). For instance, product utility would be significantly affected if the FDA reported *this device is commercially available, but there is no evidence to support X, Y and Z* (Wizemann,

2010). In summary, *there is a significant divide in the information accessible to evaluate the value, safety, efficacy, or quality of medical devices* (Abrahim & Dimick, 2017).

Background Information on FDA Regulatory Processes and Data

Before introducing our conceptual model, a review of FDA process details will be provided, specifically those for classification, post-market surveillance, recall and cease distribution and notification. In the context of these processes, it is relevant to review the case of transvaginal mesh (TVM), which lead to the only *categorical recall* in the FDA's history. The topic of biofouling will be introduced and briefly explained, as it is unique to implantable medical devices which is the focus of our research. Lastly, FDA's 510(k) database, the primary source for the work will be reviewed.

FDA Product Classification and Post-marketing Surveillance System

Per FDA.gov (n.d.), devices are evaluated and classified based upon perceived risk, with respect to expectations for safety and effectiveness. There are three classes, they are:

> *Class I* is general controls. These are healthcare tools with the least regulation. The don't help or sustain life. They don't prevent impairment. There is no unreasonable risk of illness or injury. Device examples include, but are not limited to, bandages, gloves, surgical instruments (FDA, n.d.).
>
> *Class II* is general controls with special controls, meaning general controls alone don't assure safety and effectiveness. Examples of special controls are labelling, performance standards and post-market surveillance. Device examples include, but are not limited to, acupuncture needles, powered wheelchairs, infusion pumps and air purifiers (FDA, n.d.).
>
> *Class III* is devices for which general and special controls cannot ensure safety and effectiveness. These are devices that support or sustain human life. Devices in this category require premarket approval (PMA). Device examples include, but are not limited to pacemaker, defibrillators and endosseus (bone) implants (FDA, n.d.).

Once approved by the FDA, device manufacturers can legally deliver their product to American doctors and medical institutions for usage.

Unlike drugs, which are labeled, dated, and tracked, there is no comparable system for medical devices (Lenzer, 2017). The management of on-going effectiveness of a medical device is then left to an informal network of patients, healthcare professionals, importers, manufacturers themselves and attorneys. Their concerns and experiences of adverse events (AEs), including deaths, injuries and/or malfunctions, are documented in the *Manufacturer and User Facility Device Experience* or MAUDE database. The FDA (n.d.) describes the MAUDE database as a passive (post-market) surveillance system. Contributors may be involuntary or voluntary. Manufacturers, importers and device-user facilities have mandatory reporting obligations (FDA, n.d.) Healthcare professionals, patients, consumers, and legal advisers, like attorneys, are self-selected, voluntary reporters (FDA, n.d.) The service of the content of the MAUDE database is identified by the FDA (n.d.) as three-fold:

(1) to monitor device performance

(2) to detect potential device-related safety issues, and

(3) to contribute to the general benefit-risk assessments of devices.

The effectiveness of these FDA activities and processes, as they relate to medical devices, have drawn scrutiny.

Medical Device Industry Regulations Should Include Patient Safety

When evaluated in the context of the medical device industry. Innovation's value or *goodness* could be equated with the patient experience and specifically that of patient safety. Regulation and approval processes play a role here too. Afterall, the benefits of an

unsafe medical device would be suspect with which to begin. A literature review supports this connection. Nature Medicine (2022) reports "regulatory bodies have begun to take steps to guide preclinical development, so that the formal approval process and potential market entry — which require that interventions are proven to be effective as well as safe in patients. . . ." Coiera (2004) simply declares "health innovation is the way to go in creating a more efficient and safer environment." Sellapans et al. (2013) recognize "the innovative efforts such as Computerized Physician Order Entry (CPOE), a Pharmacy Information System, automated dispensing machines and Point of Administration Systems have been carried out with the claim of improving medication safety."

In Altenstetter's (2011) economic research, one conclusion "is patient safety concerns are or should be kept alive throughout the entire regulatory cycle from clinical evaluation and premarket checks to their final use in a huge variety of clinical settings around the globe." Innovation for patient safety forges new organizational relationships. The Kidney Health Initiative (KHI) is a "public-private partnership established by FDA with the American Society of Nephrology (ASN) to advance scientific understanding of the kidney health and patient safety implications of new and existing medical products" (Archdeacon et al., 2013). KHI will serve as a forum "to facilitate dialogue and research that informs regulatory sciences with regard to kidney health and patient safety" (Archdeacon et al., 2013).

Within the European Union, new medical device regulation went into effect in 2020. This "new regulation will implement stronger patient safety requirements, including a mandatory clinical investigation where a device is evaluated in patients, a conformity assessment where the safety and performance of the device is verified by a

notified body, and the constant monitoring of incidents once the device is on the market*"* (Theinpont et al., 2020). For the International Journal of Medical Toxicology and Drug Experience, Aronson et al. (2020) advocates that "applicants for marketing authorization for a new device should have to assure regulators, from studies in patients, of its quality of manufacture, safety, efficacy, and practical usability before licensing." These sources and their research conclusions are testimony to the existing and necessary connections between innovation, regulation and safety.

Persistent Concerns for FDA's Medical Device Approval Process

Specifically, there is controversy over the effectiveness of the FDA's 510(k) process and subsequent passive, post-marketing surveillance (PMS) system in the use of MAUDE. As early as 1986, the United States' General Accountability Office (GAO) reported hospitals were not aware of most medical device problems (GAO, 1986) (Chelimsky, 1986). Some additional GAO (1986) findings were:

(1) Nine percent of the problems identified with the ten devices studied involved actual injuries

(2) Wear or deterioration of devices was the major cause of problems in one-third of the hospital reports, while other causes were defective components, design flaws, and improper use

(3) Hospitals reported only 51% of identified medical device problems to such outside organizations as device manufacturers, distributors, and independent distributors

(4) Hospitals made 83% of their reports orally and without documentation

(5) Hospitals reported more manufacturer-related problems than user-related problems

(6) Hospitals repaired or replaced defective components to avoid a recurrence of 85% of the problems they experienced

(7) 52% of the problems hospitals reported to manufacturers and distributors resulted in the repair or replacement of a failed device

(8) 53% of surveyed health care professionals were not aware of the FDA system for reporting problems.

FDA Medical Device Recall and Cease Distribution and Notification Order

Upon evaluating the medical device reports (MDRs) in the MAUDE database, the FDA can decide to recall a product, thereby removing or correcting products that are in violation of laws administered by the FDA. According to FDA.gov (2018), recalls are issued when a medical device is defective, when it could be a risk to health, or when it is both defective and a risk to health (n.d.) (Table 2.) In its evaluation, the FDA (2019) considers the following factors and more:

- *Whether any disease or injuries have already occurred from the use of the product*
- *Whether any existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard. Any conclusion shall be supported as completely as possible by scientific documentation and/or statements that the conclusion is the opinion of the individual(s) making the health hazard determination*
- *Assessment of hazard to various segments of the population, e.g., children, surgical patients, pets, livestock, etc., who are expected to be exposed to the product being considered, with particular attention paid to the hazard to those individuals who may be at greatest risk*
- *Assessment of the degree of seriousness of the health hazard to which the populations at risk would be exposed*

- *Assessment of the likelihood of occurrence of the hazard*
- *Assessment of the consequences (immediate or long-range) of occurrence of the hazard.*

Recall status is reported in the FDA's *Medical Device Recall Database*. As stated, recalls may be either corrections or removals. A *correction* is a problem with a medical device in the place where it is used or sold (FDA, n.d.), whereas *removal* addresses a problem with a medical device by removing it from where it is used or sold (FDA, n.d.). Medical device recalls are usually conducted voluntarily by the manufacturer (FDA, n.d.).

Beyond a recall, if the FDA finds that there is a reasonable probability that a device intended for human use would cause serious, adverse health consequences or death, the FDA may issue a cease distribution and notification order (FDA, 2018) (Table 2). Just as the name suggests, in the issuance of a cease distribution and notification order, the FDA requests reasonable efforts to ensure and verify all health professionals, device user facilities, consignees and individuals have been notified on the order and have been instructed to cease use of the device or take other appropriate action, so the use of the device will not cause serious, adverse health consequences or death (FDA, 2019).

Examples of Medical Device Recalls

The annual number of medical device recalls increased by 97% between 2003 and 2012, due to stepped-up public safety efforts by both regulators and industry (Shobeiri, 2019) (Eisenhart, 2014). (Figure VI.) Specifically, more recalls were placed in Class I category than earlier years (Britcher, Leone & Sergio, LLC, 2014). The top ten regulatory violations for medical device recalls classified between 2010 and 2012 were linked to

quality system concerns (Shobeiri, 2019). Examples of medical devices that have come under public scrutiny include, but are not limited to:

Allergan's Lap-bands: Lap-bands were approved based upon a lone study of 299 people, in which 51% reported chronic nausea or vomiting or both and 25% had their bands removed before the end of the three-year study because of complications or failure to lose enough weight (Consumer Reports, 2012). FDA recall posted in 2010.

Cyberonics' Aspire Seizure Response Vagus Nerve Stimulator (VNS) Therapy: Engineered to provide electrical stimulation to a patient's vagus nerve to manage seizures. Operational failures impacted battery life and resulted in failure to the point where the device induced the very conditions and symptoms it was designed to treat (Miller, 2018, Lenzer, 2017). Series of FDA recalls posted 2015, 2017 and 2018.

Boston Scientific's ProteGen Sling Collagen: A transvaginal surgical mesh (TVM) product. Categorized as Class II device, TVM went to the market with 510(k) approval, exercising the substantial equivalency regulatory guideline, tied to a predicate device given prior approval (Shobeiri, 2019) (Consumer Reports, 2011). TVM was used to assist patients experiencing medical issues from a prolapsed uterus and/or bladder (Shobeiri, 2019). The mesh can become contaminated and erode, while it resides in an organ-rich space in the body creating numerous complications compromising a patient's quality of life (Consumer Reports, 2011). Often, their only recourse has been litigation – some

estimate 3,000 cases have been adjudicated to-date, with more than 25,000 pending (Andrus Wagstaff, n.d.) FDA recall posted in 1999.

Johnson & Johnson's Pinnacle Hip Implant: Medical debris escaping from cobalt metal hip joints has been found to cause slow and profound poisoning, where recipients' mental health deteriorated to the point of induced psychotic episodes (Ziering et al., 2018). FDA recall posted in 2013.

Draeger Medical Breathing and Anesthesia Set VentStar: Distributed beginning April 2016 with FDA approval, this device provides mechanical ventilation and critical breathing support to patients (Pulmonology Advisor, 2019) (Ausick, 2019). The devices may have been incorrectly assembled resulting in a short-circuit in the breathing hose that may lead to irreversible patient harm, up to and including death (Ausick, 2019). Recalled January 25, 2019.

The above list demonstrates the necessity for FDA protective measures when medical device innovation falters.

Biological Facts: Foreign Body Reaction and Biofouling

Four of the five devices cited above are classified as an implantable. As a reminder, an implanted medical device is defined as a device inserted into the human body to replace a missing body part, support a damaged body part, or modify an important body function (Lind, 2017), as detailed in Table 5. Science tells us there is a

specific biological response to all foreign substances introduced to our bodies. Medical doctors and researchers refer to such as a *foreign body reaction* (FBR). (See definitions in Table 2.)

Table 5: The Business Environment

Agent:	Producer	Regulator	Consumer
Function:	Medical Device Manufacturer	Food and Drug Administration (FDA)	Patient Safety
Process:	Innovation	Device Approval	Device Adaption; Foreign Body Reaction Experience

FBR is the inflammatory reaction provoked by implanted materials such as a medical device (Luttikhuizen et al., 2015). Biologically, tissue cells and infiltrated inflammatory cells create a dynamic microenvironment and produce different (reactionary) chemicals such as cytokines, chemokines, and matrix metalloproteinases which in turn mediate FBR (Anderson et al., 2008). In soft tissues, FBR presents as cellular information and fibrous encapsulation (Donath et al., 1992). Investigating subcutaneous implantation sites, Luttikhuizen et al. (2006) identified a (six) staged cellular and cascading approach exercised during a body's response to a foreign substance. In sequential order, in elementary words, they are:

Activation – Spontaneous adsorbing of proteins and fiber to the implant.

Angiogenesis – Formation of new blood vessels from pre-existing vessels. It's coagulation in response to tissue's oxygen deprivation, medically identified as hypoxia.

Extravasation – Movement of leukocytes (white blood cells) to the area.

Migration – Movement of chemokines, or signaling proteins, calling more leukocytes (white blood cells) to the affected area. The immune system is actively targeting the implant.

Phagocytosis – This is the body's attempt to remove pathogens and cell debris. It is the ingestion of bacteria and other material, which at this juncture, depending upon the material of the implant, can include particles of the implant itself.

Fibrosis – Scarring, a structural cellular scaffold built in prior stages to maintain tissue integrity, is now established (Luttikhuizen et al., 2006).

In summary, the body's first immunological response to a device is to attack. For this reason, implanted medical devices are prone to infection (Mateesecu et al., 2015). One medical option is an antibiotic prescription, but while effective, antibiotics can cause gastrointestinal reactions or allergic reactions or worse – assist in the production of antibiotic-resistant bacterial strains (Mateesecu et al., 2015). Mateesecu et al. (2015) investigated the use of antimicrobial peptides (AMPs) to fight infection for medical titanium surfaces found in dental implants and prosthesis with promising results. FBR is a major impediment toward the development and long-term functionality of most implanted biomedical devices (Nichols et al., 2012). Researching subcutaneous devices, Nichols et al. (2012) found implants disrupt native tissue, as proteins and molecules adhere to the device surface. Avula et al. (2013) noted a host's FBR adversely effects the performance of numerous implanted biomaterials especially biosensors, including clinically popular glucose-monitoring sensors [for diabetes].

Harding and Reynolds (2015) agree that the inclusion of synthetic material for orthopedics, catheters, infusions lines, stents, grafts, and sutures trigger a foreign body reaction (FBR). They take it one step further stating the FBR to artificial materials often results in biofouling, a compromise of the device due to biological processes (Harding & Reynolds, 2015). Medical implants face nonspecific biofouling from proteins, cells and microorganisms, which contribute to complications and device failure which can ultimately limit the lifetime of the device (Hung et al., 2017). And increasing use of

implanted devices leads to an increase in risk for the development of device-associated infections. Harding and Reynolds (2015) estimate the bacterial infection rate associated with biofilms on device surfaces to be at 65%. Even if we were to grant 100% efficacy to an implantable device, one must be mindful, a body's immune system will respond with antagonism and infection rate is high.

Background on FDA and Transvaginal Mesh (TVM)

When the regulatory system fails, injured patients often take legal action. According to Matthew Goldstein (2019), reporting for the *New York Times*, litigation over pelvic mesh, also called transvaginal mesh (TVM), ranks as one of the biggest mass tort cases in U.S. history, in terms of claims filed, number of corporate defendants and settlement dollars. (Figure 9.) More than 108,000 lawsuits alleged that TVM mesh causes complications including pain, bleeding, infection, organ perforation and autoimmune problems (Drugwatch, n.d.). One of the largest TVM settlements to date was $830 million for 20,000 cases. As of November 2019, more than 2,263 lawsuits were still pending (Drugwatch, n.d.). Their story began in America's medical device industry 24 years ago.

Boston Scientific's ProteGen Sling Collagen was approved by FDA via 510(k) process on November 19, 1996. Per FDA's 510(k) filings, Boston Scientific's ProteGen Sling Collagen device description is a surgical fabric woven or knitted from polymer fibers and precut into patches for soft tissue reinforcement for surgical repair procedures (FDA, 1996). The device was predicated upon five substantially equivalent, existing mesh products (FDA, 1996). (Table 2.) Intended use was for implantation to reinforce soft tissue where weakness exists for the urological, gynecological, and

gastroenterological anatomy inclusive, but not limited to the following procedures: pubourethral support, urethral and vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor, bladder support and sacro-colposuspension (FDA, 1996). Diagnoses associated with these procedures include pelvic organ prolapse (POP) and/or stress urinary incontinence (SUI). Obesity, family history, hysterectomy, menopause and/or vaginal childbirth are medical facts often associated with these diagnoses (Brownworth, 2018).

It is estimated POP and/or SUI affect up to 50% of women (Brown et al., 2016). POP occurs when organs sag or fall into the vaginal canal because of weak pelvic muscles (Llamas, 2018). Usually, the bladder, uterus, rectum or bowel is involved in the prolapse. Of these, the bladder is the most common organ affected. SUI occurs when the bladder leaks urine during moments of increased physical activity that increases pressure on the bladder. Of the total population affected by POP and/or SUI, approximately 2% – 11% will undergo surgical correction in their lifetime (Brown et al., 2016). Surgical options include native tissue repair, but there are valid concerns for high recurrence rates with this approach (Sivaslioglu et al., 2008). In an attempt to overcome this concern, subsequently polypropylene mesh was used to augment the repair (Brown et al., 2016).

Given its usage, *ProteGen Sling* is considered a transvaginal mesh, or TVM, product. It is estimated that TVM has been implanted in millions of women, many of whom have experienced severe complications. Reported complications include, but are not limited to mesh erosion, open wounds, device failure (cracking, tearing), separation/retractions, scarring, protrusion, pain, infection, dyspareunia, fistula, discharge, and dysfunctional voiding of urine (Pharm3r, 2017). According to

DrugDanger.com, over 100,000 lawsuits have been filed against manufacturers of TVM devices, including Boston Scientific and subsequent 510(k) approved devices that entered the market after *ProteGen Sling Collagen* and were utilized for the same diagnoses.

On March 17, 1999, the FDA recalled the *ProteGen Sling*. Reasons cited were higher than expected vaginal erosion and dehiscence, stating the product does not appear to function as intended (Glassman, 2014). FDA now estimates about 10% of women who had vaginal mesh implanted will experience erosion within the year (Glassman, 2014). In 2011, The Institute of Medicine said the now 40-year-old 510(k) approval process is obsolete and needs to be revised in order to provide the assurance of safety and effectiveness of medical devices before they are approved to be used by the public (Mostyn Perspectives, 2016). The story of the approval and eventual recall of Boston Scientific's *ProteGen Sling* is a perfect example of the need for change (Mostyn Perspectives, 2016).

In the face of a medical device recall, the promise of medical innovation is compromised by the peril of an inferior product brought to market. But is also bodes at something potentially more sinister being innate in the process because, as noted, complaints are not just for the Boston Scientific's *ProteGen Sling,* but also all subsequent 510(k) approved devices citing *ProteGen Sling* as their substantially equivalent predicate. Patients become casualties of the failure of the FDA's 510(k) approval process to identify such high-risk devices. In 2011, As David Kessler, FDA Commissioner 1990 – 1197, has stated, "When it comes to medical devises, we've built a system that doesn't work," (Zeiring et al., 2018).

On April 16, 2019, FDA (2019) mandated a *categorical* order for all manufacturers of surgical mesh products indicated for transvaginal repair of pelvic organ prolapse (POP) to stop the selling and distributing their products immediately. This order impacted all those mesh devices conceived and approved for POP. As Jeffrey Shuren, M.D., director of FDA's Center for Devices and Radiological Health, communicated on behalf of the FDA (2019): "We've determined we need evidence that they [mesh devices] work better than surgery without the use of mesh to repair POP . . . and that evidence was lacking in these premarket applications." This occurrence, the FDA's unprecedented cease distribution and notification order for a category of device products, identified as TVM, is the point of origin and springboard for our research. Our study teases the connection between the medical device industry's innovation process and the FDA's 510(k) predicate device approval process.

Conceptual Model

Our research relies on the acknowledgment and understanding of two concepts in the FDA's 510(k) approval process: substantially equivalent (SE) and predicate device. Therefore, it is necessary to take time to understand the specific meaning of these terms in context of FDA. To begin, each corporate entity that wants to market a Class I, II or III medical device intended for human use, must submit a 510(k) form (FDA, 2020). Filing the 510(k) form is a premarket submission made to the FDA to demonstrate that the device to be marketed is safe and effective, that is, substantially equivalent (SE) to a legally marketed device (FDA 2020). The legally marketed device to which the equivalence is drawn is commonly known as the predicate (FDA, 2020). A device is

substantially equivalent if it possesses the same qualities as the predicate in the following regards:

- Has the same intended use as the predicate and
- Has the same technological characteristics as the predicate; or
- Has the same intended use as the predicate; and
- Has different technological characteristics and does not raise different questions of safety and effectiveness; and
- The information submitted to FDA demonstrates that the device is as safe and effective as the legally marketed device (FDA, 2020). (Table 2.)

The claim of substantial equivalence does not mean the new and predicate devices must be identical (FDA 2020). The FDA first establishes that the new and predicate devices have the same intended use and any differences in the technological characteristics do not raise a question of safety and effectiveness (FDA, 2020). The FDA then determines whether the device is as safe and effective as the predicate device in terms of technological characteristics and performance data (FDA, 2020). Performance data can include clinical data and non-clinical bench performance data, including engineering performance testing, sterility, electromagnetic compatibility, software validation, and biocompatibility evaluation, among other data (FDA, 2020). Until the submitting entity receives an order declaring a device SE, the submitter may not proceed to market the device (FDA, 2020). That determination is typically made within 90 days (FDA, 2020).

The FDA's 510(k) database is available online at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. Results offer a

summary page of basic information like device classification name, 510(k) number, device name, applicant, date received, decision date, among other details. (Figure 10.) While the entire 510(k) application is not accessible, a portion, which is *Section VII Summary of Safety and Effectiveness* is linked to the search results.

Our conceptual model of this activity can be found in Figure 12. This conceptual model of the medical device chain of innovation builds upon previous theories of innovation and acknowledges the foundation of FDA data and processes. It illustrates the generational sequence or chain of medical devices and their predicates. (Figure 12.) For our purposes, generation is adopted from software development in the technology industry. From personal industry experience, innovation in technology is typically a planned linear set of specific enhancements, the most recent release builds upon the last – correcting any bugs or issues while introducing new features and functionality. The literature says generations are conceived within markets and companies. Next generation products are called such *because they are expected to inspire and support a whole new line of derivative products* (Tabrizi and Walleigh, 1997). Thus, a product introduced by a single company can reset the marketplace. Albers et al. (2015) even go so far as to label product generation development as new model *that reflects the natural conditions* of product development in innovation theory. (Think: Apple's iPhone.) This proposed generic model of device innovation is based upon the fact that the 98% of medical devices in the US market being approved via the FDA's 501(k) process.

In this study, a relational view is completed (Figure 16), following the approach of Heneghen et al.' (2017), along with the generational view (Figure 14) and a temporal view by decade (Figure 15). In the temporal view, products are organized in their

chronological time order sequence by decades. This is a nod to Amabile and Pratt's (2016) declaration "creativity and innovation are bound by time". Meaning, "what appears novel in a domain today is dependent upon what already exists in that domain" (Amabile and Pratt, 2016).

To populate, the FDA 510(k) database was reviewed to apply specific devices into each generation to document the predicate devices thereby building a chain of innovation. One data item identified within each of the summaries in *Section VIII Summary of Safety and Effectiveness* is the applicant's predicate device(s). Therefore, it was possible to build a family tree of generations of innovative devices, based upon their documented predicates in the FDA's 510(k) database. Each predicate device identified is a link in a chain to the most current edition of a device. Indeed, as previously mentioned, this approach was taken by Heneghan et al. (2017) in their investigation of the device chain approval for transvaginal mesh (Figure 11). Ours is an application of the same methodology but with a different point of origin and seeking a different data structure. We want to probe the assumption of safety by starting with the identification of a contemporary generational sequence of devices. Specifically, to explore the notion of whether the case of transvaginal mesh (TVM) was an exceptional occurrence or is it just a matter of time before the next categorial cease and notification is issued for an implanted medical device? Therefore, our contribution is to introduce a generational view along with a temporal one. We're looking not only at relationships but sequence and ordering by generations and time of product innovations.

Research Methodology

To begin, a generation of origin, or Gen 0 device, was identified. Given the FDA's categorical cease distribution and notification for all transvaginal mesh (TVM), our interest remained in surgical mesh, but for use in other indications. [For instance, according to DrugWatch.com, mesh is used in nine out of ten hernia surgeries annually, and the FDA estimates more than one million hernia repairs are performed each year (FDA, 2018).] Another criterion for our Gen 0 product was that it must have a (relatively) recent date ($x < 10$ years) of approval for commercial availability. Given these parameters, we selected TELA Bio (in Malvern, PA) and their Ovine Tissue Matrix (OTM) product for our research. Following a brief conversation with the Founder, Chief Executive Officer, and President Antony Koblish, it was determined there was interest in a prospective research project. Mr. Koblish recruited Paul Talmo, TELA Bio's Chief of Strategy, and Dr. Libbe Englander, Founder and Chief Executive Officer, of Pharm3R, to provide any industry expertise required for this research project. (Pharm3R is a healthcare analytics firm that supports TELA Bio with special projects.)

As previously explained, we learned in the case of Boston Scientific's *ProteGen Sling* that each 510(k) approved device receives an approval number that starts with a K. ProteGen Sling's was K963226. (Figure 10.) TELA Bio's *Ovine Tissue Matrix* (OTM) is K141053. (Figure 13.) The original paperwork submitted to the FDA is available for review and consideration in Figure 13. This summary documentation is formatted to FDA 510(k) submission requirements and identifies the predicate device or devices and their 510(k) approval number upon which the new device is based. In this instance, TELA Bio identified one predicate: the Endoform *Reconstructive Template* produced by Mesynthes,

Ltd. with a 510(k) approval number of K130547. With this new 510(k) number, the process can be repeated. Per our construct, we aimed to identify five generations of a product. In pursuit of this, a general parameter was established to pursue a specific branch for the last 20 years or to third generation which ever came sooner. (As Amabile and Pratt (2016) write, innovation is bound by time and place.) The specific steps were:

1) Visit https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
2) In Search Database block, for *510K Number* enter the device's 510(k) approval number. (As a reminder, our first entry was K130547 for TELA Bio's Ovine Tissue Matrix.)
3) Hit Search button.
4) Confirm Search Results by 510(k) number.
5) Identify *Date Received* and *Decision Date*. Record.
6) With 'x' as our 510(k) decision date, if date is older than 20 years and x > 3rd generation, end branch. If within last 20 years and/or x ≤ 3rd generation continue to next step (7).
7) Scroll down to *Summary*. Click *Summary* hot link.
8) Search PDF of original manufacturer's submitted application for the section of *Summary of Technological Characteristics.*
9) Under the *Summary of Technological Characteristics* identify predicate device or devices, record their 510(k) number(s) for the next search(s).
10) Repeat steps 1 – 6 (or 9) as necessary.

We used post-it notes to easily manipulate the relationship among the devices as we came to better understand how the devices fit among the different branches in the

generation chain. These same post-it notes were sequenced again to produce our temporal view by decade. Also, TELA Bio secured the services of Pharm3R to electronically (versus manually) complete this family tree. The signatory project manager was Dr. Libbe Englander. In addition, notes were cross-checked with the FDA's Total Product Life Cycle (TPLC) which integrates premarket and postmarket data about medical devices (FDA, 2018). Data is assembled from the Center for Devices and Radiological Health (CDRH) databases including Premarket Approvals (PMA) Premarket Notifications [510(k)], Adverse Events and Recalls (FDA, 2018). Final results were organized and digitized. Conclusions were drawn based upon not only the relationship between the devices but also a comparison of our device innovation chain with that of Heneghan et al. (2017).

Results

The application of the conceptual model (Figure 12) to the collected data can be found in Figures 14 - 16. Figure 14 populates the generational view of our conceptual model. It documents five generations of medical device innovation from the origin device, TELA Bio's Ovine Tissue Matrix (OVT). Figure 15 populates the temporal view of the conceptual model. In this figure, the origin device is labelled as generation 0.

Based upon information from 510(k) database, there is one predicate device for TELA Bio's OVT (2014). That is the Endoform Reconstructive Template from Mensynthe (1) introduced in the same decade (2013). The Mensynthe device has three predicates. There are two in the prior decade, they are Surgisis Gold Hernia Repair Graft from Cook Biotech (2) and LRTM Surgical Repair Mesh from LifeCell (3), approved in 2006 and 2007, respectively. There is one in the 1990's, and that is another Surgisis brand

device also from Cook Biotech (4), with an approval year 1998. If we continue to follow the temporal view by decade of this family tree, like the generational view, we see not the anticipated linear lineage (of a grandparent to parent to progenitor) series of devices, but an erratic and unpredictable path which could suggest a troubling indiscriminate process of innovation within the implantable medical device industry. Finally, Figure 16 removes the generational sequence of devices and demonstrates the simple predicate relationships between devices.

Colloquially, we have spoken of these anticipated results being a *family tree* or *links in a chain*. Crudely, the research suggests, as stated above, if this was a family tree, it could be classified as incestuous; if it were a chain, it would be a tangled one! The FDA's 510(k) approval process is broken. Within the parameters we set and followed in our methodology, results are:

- Number of Predicate Devices: 15
- Number of Device Manufacturers: 9
- List of Device Manufacturers: Atrium Medical, Bio-Vascular, Cook Biotech, C.R. Bard, Davis & Geck, LifeCell, Organogenesis, Mensynthe and Tissue Science Laboratories.
- Date Range of Decision [510(k) Approval]: May 9, 1983 – May 31, 2013
- Year Range: 30
- Range of Years: 1983–2013
- Range of the Number Predicates Per Device: 1 – 3 and, of course, at least one is required.
- Number of Product Categories: 3

- Product Categories: FTL, FTM and PAI. (Descriptions below.)
- Product Category Descriptions:

  FTL: Mesh, Surgical, Polymeric

  FTM: Mesh Surgical

  PAI: Mesh, Surgical, Non-Synthetic, Urogynecologic, for Pelvic Organ Prolapse, Transvaginally Placed.

  (FDA Product Medical Device Database, n.d.)

  Source: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm.)
- Device Material Categories: Synthetic and Biologic
- Types of Synthetic: Polyglycolic acid, polypropylene and polytetrafluoroethylene.
- Types of Biologic: Bovine, ovine and porcine.

The most interesting fact in review of the above summary was the identification of a device in the PAI product category which, as defined by the FDA Product Classification database is mesh, surgical, non-Synthetic, urogynecologic, for pelvic organ prolapse, transvaginally placed. This product category is an overlap between our device map and Heneghan et al. (2017). It is significant because it suggests the innovation lineage of TELA Bio's Ovine Tissue Matrix has roots in the PAI product category associated with the unprecedented TVM recall. A first thought was: Is this product impacted by the FDA's categorical TVM cease distribution and notification? The answer is, "No." This is because, while the recorded product category includes transvaginal placement the stated intended use, per 510(k) filing, is for rectal intussusception repair or

an unfolding of the rectal wall. It appears it technically meets the FDA's PAI category requirements for its pelvic placement. But as a patient, wouldn't one be worried? An equivalent might be an auto manufacturer launching a new car model and when asked about the inspiration for their product, the company responds: One predicate device for our new hatchback automobile was the 1972 Ford Pinto.

In review of the Heneghan et al. (2017) device chain of approval for transvaginal mesh (TVM) (K963226), 50 devices were identified after 2000. An inventory was completed of unique 510(k) approval numbers to determine whether any of our 15 predicate devices crossed with those in Heneghan et al. (2017). Table 6 documents the results.

Table 6: Cross Study Inventory of 510(k) Approvals

(Heneghan et al., 2017)

In comparing unique database IDs of 510(k) numbers, no duplicates appear between the family trees. This means each tree to the generational level documented here is independent of each other.

Gen 0 Device	**TELA Bio Ovine Tissue Matrix (K141053)**	**Boston Scientific's ProteGen Sling (K963226)**
Predicate Devices by 510(k) Approval	K130547, K062697, K034039, K013625, K070560, K050355, K043366, K042026, K992556, K992991, K980431, K970561 K961810, K923657 and K830889.	K073164, K010035, K073703, K071902, K070065, K023516, K092203, K030123, K023516, K021263, K020663, K013355, K011251, K082387, K051485, K040623, K040537, K033636, K010931, K002721, K061445, K042851, K031767, K092607, K093747, K070073, K041176, K132054, K100485, K020110, K100936, K052401, K033568, K070846, K012949, K094061, K992159, K090271, K083839, K082471, K063712, K051503, K033376, K013718, K063562, K071512, K082216, K102815, K113205 and K051245.

Again, we find no predicate device overlaps. This is prima facie quantified as good. Products in the categorically recalled TVM space do not share a predicate device with TELA Bio's Ovine Tissue Matrix. However, we do observe overlap in two manufacturers: C.R. Bard and Cook Biotech. (Identified in Table 7 using **bold** text.) Specifically, the Surgisis brand name from Cook Biotech appears in both trees. (K992159 for Heneghen et al., 2017). One might become wary as to what the manufacturing distinction between one mesh product made by the same company. What separates or is the distinction of a mesh product C.R. Bard made that appeared in the innovation chain for TVM in comparison to one that appeared in the innovation chain for TELA Bio's *Ovine Tissue Matrix*?

Again, for Cook Biotech, we have a duplicate of a brand name. So, research reveals to us the same manufacturer, same mesh brand name, but (supposedly) two distinct products. One of those mesh products has been categorically banned by FDA, one has not (yet) been. Is this the mesh product you would want to see implanted in you? In your family member? Heneghan et al. did not identify the material of a device in their device chain summary, but from some of the product names [Surgical Mesh, Polymeric (K090271), *Polypropylene Mesh* (K033636) and Gynecare *Gynemesh PS Prolene* (K013718)], we can infer they would be in synthetic category with no further research. TELA Bio would argue their distinction in their source of materials, e.g. There is a category of biologic mesh. So, the predicate device stipulation seems too trite (perhaps) for the complexities of the manufacturing process – for devices to which patients are committing a lifetime of their health, safety and wellness.

Table 7: Cross Study Inventory of Manufacturers

(Heneghan et al, 2017)

Gen 0 Device	**TELA Bio Ovine Tissue Matrix (K141053)**	**Boston Scientific's ProteGen Sling (K963226)**
List of Manufacturers of Predicate Devices	Atrium Medical, Bio-Vascular, **Cook Biotech**, **C.R. Bard**, Davis & Geck, LifeCell, Organogenesis, Mensynthe and Tissue Science Laboratories.	Abbrevo, American Medical Systems (AMS), Apside Medical, Boston Scientific, **Cook Biotech**, Covidien UK, **C.R. Bard**, Ethicon, Paladin Medical, Mentor Corporation, Promethean, Sofradim and Tyco Healthcare Group.

Conclusion

This research began out of our desire to answer the question: What are the characteristics of the FDA's 510(k) approval process for medical devices? All the discovered characteristics suggest the FDA's 510(k) approval process remains seriously flawed.

The investigation of this administrative process was a proxy to better understand the innovation process. Our approach to innovation was routed in the theory and prior work of Amabile and Pratt (2017) and Albers et al. (2015), among others. Our interest was phenomenon-oriented, based upon the FDA's unprecedented categorical recall of all trans-vaginal mesh (TVM) products. Trying to ascertain the conceptual risk of a recurrence of such an event. Our methodological approach to this topic was to complete a five-generation of product family tree for a mesh product launched in 2014, TELA Bio's Ovine Tissue Matrix (OTM) modeling the research done by Heneghan et al. (2017).

In the spirit of Heneghan et al. (2017), we have produced family tree from the FDA's 510(k) data for TELA Bio's Ovine Tissue Matrix (OTM) that represents 14

medical devices over four decades. Given the findings of our first study, some general conclusions can be made.

(1) Type of Innovation: As a reminder, substantial equivalence is the FDA's requirement for premarket approval via the 510(k) process, which represents 98% of annual device reviews. Based upon this predicate dependency, theoretically, the process dictates the practices of incremental innovation at the exclusion of so many others. As a reminder, incremental innovation *is created as a result of knowledge that builds on the existing knowledge of a firm, therefore this form of innovation is competence-enhancing is products or services are created as a result of knowledge of a firm* (Naqshbandi and Kaur, 2015). Therefore, incremental innovation theory is our *best* characteristic of the FDA's 510(k) approval process.

(2) Timing: From Albers et al. (2017), we adopted a view product generation is a development process it and of itself. In addition, Amabile and Pratt declare what is perceived as innovative, is a function of time (2016). We ingested these points-of-view, in our two sequences of TELA Bio's Ovine Tissue Matrix (OTM) – *generational* and *temporal* by decade. (Figures 14 and 15.) In both views, within TELA Bio's OTM's family tree or device chain, there was not a linear path. Products often cross-referenced one another. Products in later generations referred (back) to products in an earlier one. Within the generational context, it is a little bit of one-step forward and half-step back. Within three generations, there is a leap back 16 years in one path. Yet going back five generations (but less than 30 years), in another path we find

ourselves just back ten years. The temporal view by decade reinforces the dysfunctional product development that literally becomes arrested within the scope of the family tree. Can it really be claimed that today's product is the best in utility and safety, if it references decades old technology? After all, few people drive or trust a thirty-year-old car. These time-based views reinforce the conclusion that the approval process, and by extension the innovation process, is not motivated by what patients need, but by prior market realities. Devices introduced today are moored in the devices of yesteryear.

(3) Comparison to Heneghan's Results – List of Manufacturers: Two device manufacturers appeared in both Heneghan's family tree of Boston Scientific's ProteGen Sling Transvaginal Mesh (TVM) and TELA Bio's Ovine Tissue Matrix (OTM), they are Cook Biotech and C.R. Bard.

(4) Comparison to Heneghan's Results – Brand Name: Even more damning, not only is there a duplicate of manufactures between the two family trees, but also respective one brand names: Surgisis from Cook Biotech. In balancing process and product, it appears process is winning. Efficacy is not a measurement of approval, nor does it appear to be a guideline for identifying predicates.

In our snapshot investigation, given the duplicity in product categories, convoluted predicate chains and duplicate in two mesh manufacturers and one brand name, results are not encouraging that the medical device innovation process for mesh products can reasonably ensure patient safety. Our contribution is a research-based exercise confirming anecdotal suspicions that reform of the FDA's 510 (k) approval

process is overdue and necessary. Although, TELA Bio's device chain did not immediately overlap with that of Boston Scientific's ProteGen Sling, given the incremental, minute distinctions and retro-referrals between devices, it does not mean they have to necessarily intersect to raise concerns about the process and products involved. Several questions linger:

- Is there enough distinction between mesh products used for TVM and all others to ensure patient safety?
- What of the value of innovation in medical device manufacturing?
- What are the benefits to a patient in this approval practice?

This suggests the value or inherent goodness of innovation is being corrupted, compromised, or worse, blatantly putting unaware patients at risk. At the end of the day, this implies the benefits of the innovation process are the medical device manufacturers, not the patients.

These concerns have not been adequately addressed in past research. Their ongoing presence inspires future research. Informed by the results of our first study, this highest priority seems to be to attempt to better understand the safety implications of these devices for patients. The FDA's Total Product Lifecycle (TPLC) and/or Manufacturer and User Facility Device Experience *(*MAUDE) databases play a role in supporting such further research. This is the focus of the next study to address the research question: How might the safety of 510(k) process approved medical devices be evaluated?

CHAPTER 3

BACKGROUND OF THE PROOF OF CONCEPT OF MEDICAL DEVICE SAFETY

Introduction: Assumptions and Research Questions

The public's general opinion is that medical devices are safe because they have been reviewed and approved by the FDA. Since patient safety depends on the FDA medical device approval process, the first research study examined the characteristics of the FDA's 510(k) approval process. This examination produced a linking a chain of medical devices, as traced through the FDA's 510(k) approval process, for one surgical mesh device. The most problematic characteristics of the process are that there is no linear path of progression in devices, and that there isduplication of device manufacturers and even brand names between the surgical mesh device we studied and those in the banned category of transvaginal mesh (TVM) devices. This overlap indicates an ongoing problem of the approval process. In the absence of a reliable approval process, patient safety is at risk. Forging a path for improving the flawed process is the focus of the second study.

Changes to the FDA's 510(k) approval process depend on medical, legal, and political factors. In the meantime, there is a potential to enhance doctor and patient knowledge of the relative safety of medical devices. This study investigates an option for doctors and patients to ascertain device performance. The research question is: How can the relative patient safety of medical devices approved using the 510(k) process be assessed? This question is addressed by developing a proof of concept for evaluating the relevant safety of devices in a particular category.

The proof of concept relies on publicly available data. The data sources are the FDA's Total Product Lifecyle and Manufacturers and User Facility Device Experience databases. These sources provide the recorded adverse events (AEs) or patient problems recorded for a category or mesh devices. This enables a comparison of the quantity of adverse events for an individual device and the category of devices. The proof of concept goes beyond the quantity of events to also take into account the severity of the adverse events. The severity of patient adverse events can be scaled according to the Association for the Advancement of Automobile Medicine's (AAAM's) Adjusted Injury Scale (AIS). The AAAM's AIS is a best practice tool for ascertaining the severity of an injury. Patient problems are scaled between 1 – 6 across a continuum of Minor/Moderate/Serious/Severe/Critical/Maximal. Maximal is associated with patient death. Combining publicly available data and an established injury scale provides an objective foundation for evaluating medical device safety.

The proof of concept of developing an intuitive measure of medical device safety also has relevance broader than a particular device or device category. This is conceptually explored in Figures 19 – 22. One of the basic assumptions underlying research on innovation is that the more advanced the innovation, the better the product. In the context of medical devices, it seems logical to assume that the more advanced the device innovation, the safer the device is for patients. Given that the safety of a medical device can be measured using public data on adverse events (AEs), the proof-of-concept exercise offers the opportunity to test these general assumptions regarding innovation, regulation, and patient safety.

Two Persistent Themes about Device Safety

Two themes persist in the medical device sector. First, patient safety concerns about surgical mesh continue. Given the dramatic conclusion of TVM utility, dubbed as *the scandal that rocked the world* (Kent, 2020), a wary eye has turned to other surgical mesh devices and applications. The TVM scandal suggests that surgical mesh devices for alternative (non-TVM) purposes are also potentially problematic from the patient perspective.

Hernia surgical mesh is at the top of this list because hernia repair is one of the most common surgical procedures, with over 20 million hernia repair procedures per year worldwide (Baylón et al., 2017). Hernia surgical procedures are estimated to provide $48 billion in revenue for American hospitals (Baylón et al., 2017), with Eighty percent of hernia repairs performed in the United States using mesh products (Baylón., 2017). And please note, the litigators are watching. Multiple hernia mesh lawsuits are filed with claims that the surgical mesh failed and led to severe injuries requiring revision surgery to fix (Llamas, n.d.). Michelle Llamas of DrugWatch.com reports the largest hernia mesh lawsuit settlement to date is $184 million, paid by C.R. Bard to settle roughly 3,000 cases in 2011 (Llamas, n.d.). As of March 15, 2020, there were 17,134 lawsuits pending against Ethicon, Atrium Medical Corporation and Davol Inc./C.R. Bard in just three states (Llamas, n.d.). Trials have been rescheduled multiple times because of the COVID-19 pandemic, but most trials were set to start by the end of the summer of 2022 (Llamas, n.d.).

These medical and legal developments are not surprising, given the findings of our first study, which identified the same manufacturers and brands names in the family

tree of TELA Bio's Ovine Tissue Matrix (OTM) as that of Boston Scientific's ProteGen Sling. The promise of medical device innovation is being questioned and investigated in the courts.

This new business environment reality leads to a second persistent theme: materials matter. The material composition of devices is relevant for patient safety. Identification of *material* is a required data field in a company's 510(k) documentation. As previously discussed, when it comes to implantable devices, like surgical mesh, the body's physiological response is to attack (Avula et al., 2013; Baylón et al., 2017; Harding and Reynolds, 2015; Mateesecu et al., 2015). The introduction of a foreign material into the body triggers a response characterized by one of three stereotypical reactions: (1) destruction or lysis, (2) inclusion or tolerance, and (3) rejection or removal (Baylón et al., 2017).

In the academic literature, there are multiple studies suggesting that the composition or raw material(s) of medical devices can influence performance and patient experience. Woodward (2014) says for more than 40 years platinum alloys have been employed extensively in a range of permanent implantable electronic devices and components. Woodward (2014) continues that lessor known platinum group metals (PGMs) such as palladium and iridium are viable complements to platinum and should be first choice for device companies seeking a proven and reliable metal that is biocompatible, radiopaque and electronically conductive. Chen et al. (2014) tout the benefits of gold for bioimaging and drug delivery saying gold has excellent biocompatibility and reduces side effects and toxicity levels. Basak et al.'s (2009) work suggests a coat of polyester urethane that can accommodate antibiotics within or on an

implant can increase a device's incompatibility and decrease bacterial adherence and thereby reduce the possibility of infection. Tomayer and Dupard (2011) acknowledged the benefits of silicone parts in medical devices are numerous: high elongation, heat stability, consistent mechanical properties across a range of temperatures, transparency, colourability, ultraviolet (UV) resistance, ageing resistance and environmental compatibility. However, at the same time, the use of silicone makes it challenging to conjugate material selection, complete part design, and determine appropriate manufacturing methods (Tomayer and Dupard, 2011). Ayoub et al. (2012) identified stainless steel (SS 304L) electrodes as a viable alternative to nickel electrodes in electrochemical sensor devices for early risk detection of diabetes. Goering and Galloway (1989) say toxicities of medical device materials must be examined because of the unique relationship materials have with the evaluation of a medical device's safety, their potential requirement for novel testing methodologies and, subsequently, implications to future research. Morais et al. (2010) report the degree and extent of foreign body response (FBR) depends upon the properties of the devices such as (a) composition, (b) contact duration, (c) degradation rate (d) morphology, (e) porosity, (f) roughness, (g) shape, (h) size, (i) sterility and (j) surface chemistry. Appropriate selection of biocompatible coating materials for use with implantable devices can minimize the body's negative response, while maintaining implantable device functionality and longevity (Morais et al., 2012).

Although none of the above studies examine mesh materials, they point to the importance of the type of materials used in implanted devices. The relative safety of these materials for specific uses is an ongoing concern. As shown in the research scaffolding of

Figure 17, the safety of different categories of materials in implanted devices is an important area for future research.

Overall, the focus of the two themes is on avoiding harm to patients. Innovation is expected to lead to incrementally improved products. Regulation and lawsuits are expected to keep unsafe products and materials away from patients. The industry is expected to learn from the previous adverse experiences of patients. These expectations drive the proof-of-concept research exercise to evaluate surgical mesh medical devices from the patient safety perspective.

FDA Data and the Medico-Legal Context

For evaluating medical devices, a first consideration is the availability of data. Given the highly regulated nature of the industry, data are available. The FDA's Center for Device and Radiological Health (CDRH) maintains the Total Product Life Cycle (TPLC) database (FDA, 2022). The TPLC is fed by multiple FDA data sources (see Table 8).

Table 8: TPLC Data Sources

(FDA, 2020)

Title	Description	Updated
Premarket Approvals (PMA)	Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of all devices classified as Class III devices. An approved Premarket Approval Application (PMA) is, in effect, a private license granted to the applicant for marketing a particular medical device. This database is updated on a monthly basis.	Monthly
Premarket Notifications (510(k)s)	Medical device manufacturers are required to submit a premarket notification or 510(k) if they intend to introduce a device into commercial distribution for the first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected. Some firm names may not be the current 510(k) owner. The Premarket Notification database is not updated when 510(k) ownership transfers from the original sponsor to other firm. The database is updated monthly.	Monthly
MAUDE (Manufacturer and User Facility Device Experience)	MAUDE data represents reports of adverse events involving medical devices. The data consists of all voluntary reports since June, 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August, 1996. MAUDE data is reported by patients, physicians, facilities and the device manufacturers. Preliminary, supplemental and duplicate reports exist.	Monthly
Manufacturer Name Consolidation	Applicant/Sponsor/Manufacturer Firm names are not provided with consistent spelling or abbreviations in the MAUDE database. To aggregate the information all firm names have been simplified and consolidated. As data in MAUDE improves, firm names will become the firm name in the registration database.	Monthly
Recalls of Medical Devices	This database contains a list of classified medical device recalls since November 1, 2002. Although the recall database is updated frequently as items become available, it is merged with the TPLC data on a monthly basis.	Integrated Monthly

The TPLC database "integrates premarket and postmarket data about medical devices (FDA, 2022). It includes information pulled from CDRH databases including Premarket Approvals (PMA), Premarket Notifications (510[k]), Adverse Events, and Recalls (FDA, 2022). The TPLC database is searchable by device name or product code to gain reports on particular product lines (see Figure 20). The FDA databases provide information that is utilized in the business community as part of the product development process. The FDA data is also used in the medical and legal communities.

Precedent from Medico-Legal Literature

FDA data has been used for medical decisions, and the legal community has also used FDA data as evidence in criminal cases and civil lawsuits. In this context, the focus is the patient. There is precedent in the medico-legal literature for assessing patient safety through injury and hardship via a hierarchical scale of severity.

Here are a few of the many examples in the literature. Kelly et al. (2017) conducted research on the consistency of results between different medical practitioners applying the Genital Injury Severity Scale (GISS) which quantifies and qualifies genital injury after sexual intercourse for forensic purposes. Similarly, Radojevic et al. (2015) applied an Injury Severity Score (ISS) to 47 individuals who were in a bus roll-over accident which resulted in 18 fatalities. Subedi et al. (2014) applied an Abbreviated Injury Scale for their investigation of abdominopelvic trauma patients who ultimately died, resulting in identifying a relationship between the length of time to start treatment and an increase in fatality. With respect to head injuries, Jennett (1976) identified various methods to assess severity and warned no one scale is appropriate for all types of injury or in all circumstances. Adverse Event Profiles, an exhaustive documentation of adverse events associated with a medical condition or situation, can be a tool to document these occurrences (Zaccara et al., 2011; Zaccara, et al., 2013; Mesfin et al., 2016).

Although adverse events data have been widely used, and injury scales have been widely used, there has been little prior effort to integrate them in a manner that offers transparency on medical device safety. This spurs the proof-of-concept approach in our study. The objective is to apply an established injury scale to data in FDA's TPLC database (see Figure 19).

TPLC's FTL Product Category

The FDA's TPLC database is organized by product category and, as previously stated, is a compilation of several databases which results in a collection of all reported adverse events (Table 7). Given TELA Bio's family tree, the two potential FDA surgical mesh product categories for investigation are FTL (Mesh, Surgical, Polymeric) and FTM

(Mesh Surgical). Since 2021 medical device records (MDR) TPLC data entries totaled approximately 23,000 for FTL and 500 for FTM (Figure 18.) For the purpose of the proof-of-concept exercise, the focus is on the FTL product category. Reports are identified as either device problems or patient problems or both. Since 2021, there are approximately 70 categories of device problems and 100 categories of patient problems. Therefore, patient problems become a proxy for the patient's safety. The TPLC database includes the frequency of each recorded problem. Two examples of device problems are: material deformation (210) and migration or expulsion of device (900). Two examples of patient problems are: swelling/edema (323) and bowel perforation (41).

Methodology

The methodology involves the application of an established injury scale to data in FDA's TPLC database "Scaling is the assignment of objects to numbers according to a rule," said S. S. Stevens (Trochim et al., 2016, 147). Its most common application is to represent a construct using a single score (Trochim et al., 2016, 148). Scales are either absolute, arbitrary, relative or normalized (Kamat, 2019). According to Kamat (2019), seemingly arbitrary units collected in the same manner can be compared relative to each other to identify a trend. Relative scales consider and rank both the tangible and intangible (Saaty, 1993). To Saaty (1993), when building a relative scale, the goals are:

1) *To provide judgments on the relative importance of occurrences*
2) *To ensure judgments are quantified to an extent which also permits quantitative interpretation*.

A way to do this it to derive a set of weights associated with occurrences (Saaty, 1993).

The methodology of the proof of concept relies on the assessment of patient safety. Individual occurrences are the patient problems recorded for the FTM category in the TPLC database. Each reported problem is defined via the F.A. Davis Company's Taber's Cyclopedic Medical Dictionary. Taber's is available online. The 23rd edition and has over 75,000 medical diagnosis entries. Based upon definitions associated with the recorded patient problem, each patient problem is considered using the medical injury categories established by the Association for the Advancement of Automotive Medicine's (AAAM's) Adjusted Injury Scale (AIS). (Figures 18 - 20.) This is primarily because AAAM's AIS is the most popular and is considered the original (AIS) from which all others are derivative (Rautji et al., 2006). Each band increases in severity: minor, moderate, serious, severe, critical, and lethal (Franklyn & Lee, 2017; Baker et al., 1974). The diagnoses definitions are then coded per AAAM guidelines to align with the AAAM's established severity level (Miles & Huberman, 1994; Ryan & Bernard, 2000). For analysis purposes, frequency is calculated as the percentage of a specific problem at its corresponding scale of severity compared to the total of all problems recorded for scale of severity.

First, the product category total is calculated. Next, for our proof-of-concept exercise, we repeat the process for a specific device. The intent is to compare and evaluate the proportion of each patient problem to its corresponding level of severity on the scale (see Figures 18 to 20). Again, the idea is once the scale is adopted, it can be applied to measure individual devices against the whole device category. It can also be used to compare individual devices to each other, devices produced by one manufacturer with another and/or devices manufactured using specific materials in comparison to

others. In doing so, a snapshot of patient safety has been quantified with respect to implanted surgical mesh medical devices.

A quick example might be helpful here. The FDA's Total Product Lifecycle (TPLC) database records for product category FTL documents 27,272 reports for 2021 and 2022 combined. (This breaks down to 16,286 reports in 2021 and 11,436 reports in 2022.) Within those approximately 27,000 reports, TPLC identifies 70,626 adverse events (AEs). There are between 2 – 3 AEs per report (70,626 divided by 27,272). Each of these AE's has been coded by FDA into one or more categories of 100 patient problems. Sample patient problems for FTL category of mesh devices can include fistula, hematoma, urinary incontinence and 97 others for the years 2021 – 2022. Taber's 23rd Medical Dictionary defines hematoma as *a swelling comprising a mass of extravasated blood (usually clotted) confined to an organ, tissue, or space and caused by a break in a blood vessel* (Venes, 2017, p 1091). There are 255 instances reported of hematoma AEs in the years 2021 – 2022. Next, we turn to Association for Advancement of Automotive Medicine (AAAM's) Adjusted Injury Scale (AIS) (2015) and look for *hematoma*. The AAAM's AIS is organized into ten chapters by body section. Hematoma appears in several areas because it can be experienced in various parts of the body. Three of the many location examples are: Abdomen – Whole Area, Abdomen – Internal Organs, and Face - includes Eye and Ear Whole Area (Association for Advancement of Automotive Medicine, 2015, p 22, p 56 and p 51). In each of these locations, a hematoma is assessed a 5 out of 6 on AAAM's AIS. The 5 category is described as *critical* (Association for Advancement of Automotive Medicine, 2015, p xv).

This process was repeated for the remaining 99 diagnosis of AEs for FTL product category found in FDA's TPLC database. Cumulatively, then, we see how the AIS applies to the category of devices. In comparison, to complete our proof of concept, we repeated this methodology to include a specific device. Then compared the data to determine if this specific device performs the same as, above, or below the standards of the entire FTL category of mesh devices.

This methodology builds on the first study of the dissertation. In that study, it was established that the 510(k) approval process, does not always lead to better products. One of the most startling realizations was the discovery that the same manufacturers and brand names appeared in the family trees of both TELA Bio's Ovine Tissue Matrix (OTM) and Boston Scientific's ProteGen Sling. In addition, the temporal view by decade suggests a circuitous and maybe even backwards-looking sequence of new device development. To build on this in this second study, we reference the FDA's TPLC database for both a product category of devices and a specific device. We demonstrate a proof of concept for the evaluation of the relative safety of comparable medical devices. This introduces a methodology and tool for patients to make informed decisions about their healthcare regarding choice of medical devices.

CHAPTER 4

PROOF OF CONCEPT: APPLICATION AND EVALUATION OF AN ABBREVIATED INJURY SCALE (AIS) TO PATIENT PROBLEMS WITH MEDICAL DEVICES

In Chapter 3, the background was established to motivate the development of a proof of concept for evaluating the relative safety of medical devices. It is time to turn now to the specific application. In this chapter, details are provided on the application of an existing and medico-legal revered Abbreviated Injury Scale (AIS) to publicly available FDA data on the surgical mesh product category FTL. To develop a proof of concept that has potential for future applications, the scale was applied to a specific device: Ethicon's PROCEED Ventral Patch (PVP) Medium (6.4 cm x 6.4 cm) Mesh. This is a highly relevant application, since Ethicon's PVP Medium Mesh is regularly used in hernia operations.

Research Methodology

To complete the research exercise, we relied upon several healthcare industry public resources. Those were the FDA's Total Product Lifecycle (TPLC) database, the FDA's Manufacturer and User Facility Device Experience (MAUDE) database, F.A. Davis Company's Taber's Cyclopedic Medical Dictionary (Taber's) (23rd edition) and the Association for the Advancement of Automotive Medicine's (AAAM's) Abbreviated Injury Scale (AIS) (2015 edition). Following is a review of our process.

First, we accessed FDA's Total Product Lifecyle (TPLC) database for all patient adverse events recorded for the FTL (surgical mesh) product category for the years 2021 through 2022 (Figure 18). This is an involuntary and voluntary reporting record of all patient complaints for all surgical mesh products from all manufacturers. There were

27,724 records filed for FTL category products in 2021 and in 2022. (This equates to approximately 16,000 in 2021 and 11,000 in 2022.) Each record documents one or more adverse event (AE). Adverse events (AEs) are referred to as patient problems in common vernacular. Each of these adverse events (AEs) has been medically coded by the FDA based upon diagnosis/es into two or more patient problems. Between 2021 – 2022, across the 27,724 records, 70,626 individual problems have been identified. This means there are between two to three AEs associated with each filing (70,626 problems/27,724 reports = 2.54 problems per report). Of the 70,626 problem entries, 324 were attributed to *failure of implant*. Since our focus is patient problems, not device performance, we removed these entries from the count leaving a total of 70,302 reports of patient problems for the FTL product category between the years 2021 and 2022 to evaluate.

These 70,302 patient problems across 27,724 reports were medically coded into one or more of 100 specific patient problems. Table 9. Two examples of patient problems are swelling/edema (recorded 323 instances) and bowel perforation (recorded 41 instances). For the next step, the 100 patient problem categories [Column title: *Patient Problem* (TPLC)] and the associated number of medical devices (MDVS) with this problem [Column title: *MDVS with this Patient Problem* (TPLC)] were transferred into a Microsoft Excel file spreadsheet (*Proof of concept Medical Device Part I*

Table 9: Definition, Volume and Abbreviated Injury Scale of Patient Problems for FDA Product Category FTL 2021 - 2022 (Excerpt)

(FDA's Total Product Lifecyle (TPLC) Database; F.A. Davis Company's Taber's Cyclopedic Medical Dictionary 23rd Edition and Association for the Advancement of Automotive Medicine (AAAM) Abbreviate Injury Scale (AIS) 2015)

Definition, Volume and Abbreviated Injury Scale of Patient Problems for FDA Product Category FTL for 2021 – 2022						
Patient Problem (TPLC)	**Term Selected (Taber's Medical Dictionary 23rd Edition)**	**Definition Page Number (Taber's 23rd)**	**Definition (Taber's 23rd)**	**MDVS with this Patient Problem (TPLC)**	**Percentage Calculation**	**Abbreviated Injury Scale (Part II)**
Pain	Pain	1735	As defined by the International Association for the Study of Pain, an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage. Pain includes the perception of an uncomfortable stimulus and the response to that perception.	13,072.00	18.59%	9
Abdominal Pain	Pain	1735	As defined by the International Association for the Study of Pain, an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage. Pain includes the perception of an uncomfortable stimulus and the response to that perception. Pain in abdominal area of body.	746.00	1.06%	9
Hernia	Hernia	1119	The protrusion of an anatomical structure through the wall that normally contains it.	5,077.00	7.22%	5
Adhesion(s)	Adhesion	50	A fibrous band of scar tissue holding parts together that are normally separated, as within the peritoneal cavity after surgery or penetrating injuries.	4,785.00	6.81%	2
(Unspecified) Tissue Injury	Tissue	2355	Injury to tissue. Tissue specified as: A collection of similar cells and their intercellular substance that perform a particular function. The four major groups of tissue are the epithelial, connective, muscular, and nervous tissues.	3,630.00	5.16%	5

Each patient problem was referenced in Taber's medical dictionary and the specific term, its definition and page number were recorded [Column titles: *Term Selected, Definition Page Number and Definition* (Taber's 23rd)]. In addition, a *Percent Calculation* column was added to determine the percentage of the total each problem represented. The numerator was the MDVS with this patient problem and the denominator was the total patient problems reported. The source for the column titled *Abbreviated Injury Scale (AIS)* (Part II) is the second spreadsheet labeled *Proof of concept Medical Device Scale Part II*.

There were also two tabs created in the *Proof-of-concept Medical Device Scale Part I* spreadsheet. Each tab represents a year, either 2021 or 2022. (They are labelled *Patient Problems by Product 21* and *Patient Problems by Product 22*.) The source of the content here is the FDA's Manufacturer and User Facility Device Experience (MAUDE) database. The product is Ethicon's PROCEED Ventral Patch (PVP) Medium (6.4 cm x 6.4cm) Mesh. A search was done by manufacturer (Ethicon), by product (PVP Medium Mesh), by the years 2021 and 2022 (see Figure 23). This returned 440 records (211 in 2021 and 229 in 2022), representing 1.6% of the FTL product category. Each dated report was reviewed. Patient problems were tallied in a spreadsheet and totaled. See Table 10 for an excerpt.

Table 10: Patient Problems 2021Ethicon PVP Medium (6.4 cm x 6.4 cm) Mesh (Excerpt)

(FDA's Manufacturer and User Facility Device Experience (MAUDE) Database)

Date Report Received (MAUDE)	Report Number (MAUDE)	Adhesion(s)	Inflammation	Diarrhea	Nausea	Pain	Chills
12/29/2021	2210968-2021-13060	1	1	1	1	1	1
12/29/2021	2210968-2021-13057	1	1			1	
12/29/2021	2210968-2021-13055	1	1			1	
12/29/2021	2210968-2021-13054	1	1			1	
12/29/2021	2210968-2021-13053	1	1			1	
12/29/2021	2210968-2021-13049		1		1	1	
12/29/2021	2210968-2021-13048		1		1	1	
12/29/2021	2210968-2021-13046		1		1	1	
12/29/2021	2210968-2021-13043	1	1			1	
12/27/2021	2210968-2021-12997		1		1	1	
12/27/2021	2210968-2021-12994		1		1	1	

Proof of concept Medical Device Scale Part II began with the identification and definition of *Patient Problem* from FDA's Total Product Lifecyle database and Taber's definitions (Column titles*: Term Selected, Definition Page Number and Definition*) lifted from *Part I* spreadsheet (Table 9). Next, we identified which specific patient problem term was searched for within the Abbreviate Injury Scale (AIS) directory (Column title: Abbreviated Injury Search Term). Table 11 is an excerpt.

Table 11: FDA's FTL Product Category Patient Problems Scaled (Excerpt)

FDA's Total Product Lifecycle, F.A. Davis Company's Taber's Cyclopedic Medical Dictionary 23rd Edition and Association for the Advancement of Automotive Medicine (AAAM) Abbreviate Injury Scale (AIS) 2015

FDA's FTL Product Category Patient Problems Scaled								
Patient Problem (TPLC)	**Term Selected (Taber's Medical Dictionary 23rd Edition)**	**Defintion Page Number (Taber's 23rd)**	**Definition (Taber's 23rd)**	**Abbreviated Injury Scale Search Term (AAAM AIS)**	**AIS Search Term No. of Mentions (AAAM AIS)**	**Sample Terms Mentioned (AAAM AIS)**	**Abbreviate Injury Scale Rating Found (1 - 6 & 9)**	**Abbreviated Injury Rating Assigned (1 - 6, 9)**
Unspecified Tissue Injury	Tissue	2355	Injury to tissue. Tissue specified as: A collection of similar cells and their intercellular substance that perform a particular function. The four major groups of tissue are the epithelial, connective, muscular, and nervous tissues.	Tissue	57	Tissue damage, tissue loss,		5
Unspecified Infection	Infection	1242	A disease caused by microorganisms, esp. those that release toxins or invade body tissues.	Infection	term not found			5
Disability	Disability	690	Any physical, mental, or functional impairment that limits a major activity. It may be partial or complete.	mpairmen	37	Permanent, complementar	**5**	5
Swelling/ Edema	na/Edemas/Ede	Swelling-2286 Edema-935	Swelling- An abnormal transient enlargement, esp. one appearing on the surface of the body. Edema- A local or generalized condition in which body tissues contain an excessive amount of tissue fluid in the interstitial spaces.	edema	24	brain swelling/edem a, brain	**5**	5
Nerve Damage	Nerve Injury	1610	Causes of nerve damage: direct trauma, repetitive motion injuries, compression by neighboring structures, glycosylation, infections, drugs, toxins, and paraneoplastic syndromes. Symptoms: paresthesias, loss of sensation and position sense, impaired motor function, cranial nerve malfunction, changes in reflexes, and impairments in glandular secretion.	erve injur	5	nerve injury in neck, upper extremity, axillary nerve, digital nerve,median nerve, radial nerve, ulnar	**5**	5

The AIS directory based upon medical severity assigns a value between 1 – 6 to each of the patient problems, corresponding to minor to maximal (see Table 12). Problems for which there is insufficient information, per Association for the Advancement of Automotive Medicine's (AAAM's) procedures, were identified with a 9/Unknown.

Table 12: Association for the Advancement of Automotive Medicine (AAAM's) Abbreviated Injury Scale (AIS)

(Association for the Advancement of Automotive Medicine, 15)

AIS Code	Description
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximal
9	Unknown

An electronic search of each patient problem was completed (see Table 11.) The number of times a term appeared was recorded (Column title: *AIS Search Term Number of Mentions*). Examples of term mentions were also documented (Column title: *Search Terms Mentioned*). Sometimes searchable terms for Abbreviated Injury Scale (AIS) directory varied slightly from the text of patient problem found in FDA's Total Product Lifecycle (TPLC). Appropriate adaptions were made. Taber's definitions were helpful. For example, bladder frequency (TPLC) is medically referred to as bladder instability by AIS. Another example is nerve damage (TPLC) appears as nerve injury by AIS. In comparing the two sources, there was more attention to clinical detail within the AIS directory in comparison to FDA TPLC database. This makes sense as the original data source for many of the involuntary reports for the FDA are filed by laypersons with no formal medical training.

If a patient problem appeared in the Abbreviated Injury Scale (AIS) directory with one assigned code, that was the code transferred to our database. If a problem appeared in the AIS directory with more than one assigned code, per AIS guidelines, conservatism is valued, so the lesser (or least) of the codes was chosen. An example here is *thrombosis*. It

was found 28 times in the AIS directory. The assigned AIS scale level varied, including 1/Minor, 2/Moderate, 3/Serious, and 5/Critical. Therefore, 1/Minor was the recorded level for our purposes. If there was not a direct or *almost* match identified, then standard AIS coding guidelines were consulted. This determined the scale number based upon general medical application of localized, regional or systemic concerns, with consideration given for any permanent loss or damage of an organ or ability to be higher on the scale.

Results

The results of the proof of concept can be described for the entire FTL product category, and for the specific focal surgical mesh product. Table 13 presents the adverse events for the entire FTL product category, along with the AIS injury scale value. Each of the 100 conditions were assigned to one of the 7 AIS codes for the entire FTL product category. A percentage share can be found in Figure 26.

The adverse events of pain and abdominal pain require special handling. This is a typical challenge. Throughout the medical community, pain is difficult to quantify because individual thresholds for pain varies. The most prevalent scale to ascertain pain is The Wong-Baker Faces Pain Rating Scale of one to ten with a big smiley face at one end and a tearful frown face at the other. For this reason, from a litigation perspective, pain is an advised entry on almost every report. While we want to preserve these problem entries, it is not appropriate to apply them to the Abbreviated Injury Scale (AIS) scale in any category other than 9/Unknown.

Table 13: FTL Category's Reported Adverse Events by Abbreviated Injury Scale (AIS) 2021 – 2022

(FDA's Total Product Life Cycle and Association for the Advancement of Automotive Medicine's (AAAM's) AIS15)

Minor 1	Moderate 2	Serious 3	Severe 4	Critical 5	Maximal 6	Unknown 9
Chill(s) Constipation Decreased appetite Dermatitis Diarrhea Discomfort Dysuria Fibrosis Hypersensitivity Itch Local reaction Nausea Numbness Rash Seroma Scar (tissue) Spasm Thrombosis Weak (muscle) Weight (change) Vomit(ing) 21	Abdominal distention Adhesion Discharge Dysphagia Fatigue Fistula Healing (impaired) Hematuria Hypertension Node Obstruction/ occlusion Skin inflammation Sleep disorder (dysfunction) 13	Corneal pannus Dyspareunia Fever Neuropathy Ulcer Vaginal discharge 6	Erosion Erythema Foreign body reaction Inflammation Radiation syndrome 5	Abscess Ambulation difficulties Ascites Bacterial infections Bladder instability (frequency) Bowel perforation Cellulitis Cyst(s) Disability Deformity/Disfigurement Dehiscence Edema Erosion Granuloma Hematoma Hemorrhage (bleeding) Hernia Hypotension Incontinence (unspecified) Infection Internal organ perforation Intestinal perforation Ischemia Micturition urgency Necrosis Nerve injury (damage) Paresthesia (burning sensation) (2) Perforation Peritonitis Peripheral edema Pleural effusion Post operative wound infection Pneumonia Prolapse Pyorrhea (purulent discharge) Sepsis (septic shock) (2) Sexual dysfunction Skin infection Surgical site infection(s) Tissue injury Urinary incontinence Urinary retention Urinary tract infection 45	Death 1	Abdominal pain Clinical (code) not available Depression Distress Emotional change Generalized anxiety disorder Injury Insufficient information Pain 9

Another patient problem identified as a 9/Unknown was *clinical code not available.* Again, we want to recognize a problem existed as someone took the time to

complete a report, but details are lacking. Problems identified as a 9/Unknown cannot be scaled in the AIS directory. Also, a series of problems are ascribed as psychological, not physiological. The psychological and physiological states of being make a whole person's experience, but the AIS directory is focused upon the physiological. This means reports of *depression, general anxiety disorder, distress*, and *emotional changes* were each 9/Unknown. Generic *injury* and *insufficient information* problems were also assigned to 9/Unknown.

Generally, by following Table 10 from left to right, there is an increase in severity of patient problems. The most entries are in the 5/Critical category. This makes sense, as the motivation to file a report about one's device experience is probably in direct proportion to the severity of the experiences associated with that device. In 5/Critical, it became apparent that loss and impairment, like *disability, disfigurement, ambulatory* ability and *bladder/urinary* control realities. All would have potential to impact a patient's quality of life. Infections of different kinds also appear here like *wound, sepsis, bacterial* and *abscess*. And perhaps it goes without saying that holes or *perforation(s)* in any part of the body, like bowel or organ, are critical. Another problem theme that persists in the records is swelling. Swelling is bad, it is an indicator that something is wrong and the body is unable to maintain its regular functions.

We completed the same exercise for the specific surgical mesh product, the Ethicon PVP Medium Mesh product. The most interesting way to consider this Ethicon product data is to compare it to the data for the entire FTL product category. Ultimately, a representative or user of Ethicon products would want this implanted mesh device to appear a better and more reliable device than others on the market. The analysis produced

a subset of the entire FTL category. In the two years of data considered, while there were 100 total entries for FTL product category, there are 35 total for Ethicon. This means there are some problems within the category of all FTL products that have never been reported by a patient with an Ethicon PVP Medium Mesh implanted medical device. And even more importantly, there are no recorded deaths between 2021 – 2022 for Ethicon PVP Medium Mesh device. The distribution by scale number can be found in Table 14. A percentage share view is found in Figure 27.

Table 14: Ethicon Medium Mesh Reported Adverse Events by Abbreviated Injury Scale (AIS) 2021 – 2022

(FDA's Total Product Life Cycle and Association for the Advancement of Automotive Medicine's (AAAM's) AIS15)

Minor 1	Moderate 2	Serious 3	Severe 4	Critical 5	Maximal 6	Unknown 9
Chill(s) Constipation Decreased appetite Diarrhea Discomfort Fibrosis Nausea Numbness Seroma Scar (tissue) Weight (change) Vomit(ing) 12	Adhesion Discharge Fatigue Fistula Healing (impaired) Obstruction/ occlusion 6	Fever 1	Erosion Inflammation 2	Abscess Bowel perforation Cellulitis Edema Erosion Granuloma Hemorrhage (bleeding) Hernia Infection (unspecified) Necrosis Perforation Pyorrhea (purulent discharge) 12		Abdominal pain Pain 2

Another way to look at the same data would be in a comparison bar graph. Figure 28 provides that view. This is an interesting perspective for three general reasons. First, as already mentioned, there are no entries for 6/Maximal which is associated with patient death. Second is the significant difference in reported volume of Abbreviate Injury Scale (AIS) 5/Critical. There were 45 entries for the FTL product category and 12 for the Ethicon PVP Mesh device. This is over 70% difference. Directionally, this suggests that

the Ethicon PVP Medium Mesh device serves patients better than the collective family of mesh devices. The third interesting fact is that 3/Serious drops from 6 problems in FTL to just 1 for Ethicon PVP Medium Mesh. And of the problems listed in the category, one of the more benign (fever) appears for Ethicon's PVP Medium mesh.

Conclusions and Insights

The analysis of adverse events and severity of injury provides several key insights. This analysis indicates that the 3/Critical category can be seen to be a potentially intriguing scale level. The activity of economic quantification per the themes found in Porter's *Trust in Numbers* tome lurk. With every medical procedure and all medical devices there are associated risks. For treatments there is always a cost-benefit equation to calculate. Does the data imply that the potential tipping point of risk for all surgical mesh devices the patient problems reported may be 3/Serious? When the Abbreviate Injury Scale (AIS) protocols were followed, six problems were at the 3/Serious level: *Corneal pannus, dyspareunia, neuropathy, ulcer, and vaginal discharge*.

Of these six, three gave special pause. The first is *dyspareunia*, which is pain before, during or after sexual intercourse. The pain reference makes it nebulous, but it is related to a specific activity. Dyspareunia can lead to a patient abandoning sexual activity altogether. Such a loss for many patients, especially of a younger age, would likely be considered 5/Critical. But because the diagnosis is on a scale, it is assigned to 3/Serious. The second is *neuropathy* – nerve damage outside of the brain or spinal cord. This too could be a stepstone to nerve damage in 5/Critical. And *vaginal discharge,* if it becomes *purulent,* is also a notable step on a scale of intensity here. With no actual patient files to consider, this raises the question: How often do 3/Serious patient problems like

dyspareunia, *discharge* and *neuropathy* escalate and develop to be more chronic like those problems found in 5/Critical?

One of the concerns some researchers have about using MAUDE-sourced data is that one never knows the entire universe of implanted devices for which these patient problems are being reported. So, to draw a conclusion from this data, only to realize it is just 3% of all implanted devices is not equitable. One way to address this concern would be to look at the patient problems (numerator) as a percentage of all patient problems (denominator) reports and compare shares. This view is found in Figures 25 - 27.

The most compelling information presented in Figures 25 is that if it is accepted that the 3/Critical level serves as a tipping point for problems that are more impactful to a patient's quality of life, then it follows that the cost-benefit equation tolerance for 1/Minor and 2/Moderate should be the focus. When comparing FTL to Ethicon problems as a percentage of Abbreviate Injury Scale (AIS) whole, FTL product category is 22.5% of patient problems are 1/Minor or 2/Moderate and Ethicon PVP Medium Mesh product is 58% of patient problems are 1/Minor or 2/Moderate. Figure 26. On the other end of the scale, approximately 28% of patient problems in FTL product category are 3/Serious, 4/Severe, 5/Critical or 6/Maximal. Whereas only approximately 14% of patient problems for Ethicon PVP Medium Mesh are scaled as 3/Serious, 4/Severe, 5/Critical or 6/Maximal. Figure 27.

Now the question becomes: Why? Should attribution be given solely to the device or are there other factors like surgeon's experience, surgeon's technique, manufacturing or packaging details, patient lifestyle or other factors that also influence patient outcome? We must permit for the *other factors,* but the data provides justification for starting with a

proven medical device. The documentation here of the experience of patients living with the device is a position with credence and value.

Another view of the same data has been presented in Figure 28. An arc has been used to illustrate the data relationship, not just between the scale numbers (1 – 6 and 9) but also the fact that the data source mirror each other in the reverse. High percentage share of Ethicon in 1/Minor trades-off with high percentage share of FTL for 9/Unknown. And, as previously mentioned, there is a suggestion that the 3/Critical level seems to be an interesting turning or tipping point for surgical mesh.

The overall contribution is that the proof of concept survived. There is a way to evaluate patient safety. The future applications are significant because it enables a way to distinguish between manufacturers, brand names, materials and other device characteristics in their performance and impact to patient safety. This approach can be used by the business community, the medical community, the legal community, and by the most important stakeholder – patients and their advocates.

CHAPTER 5

CONCLUSION

This dissertation has been an investigation of the tension between product innovation, government regulation and public safety in the American healthcare industry. It was organized in two parts, the second built upon the first. It began with an exploration of the FDA's current and dominant 510(k) approval process, the chain of innovation precipitated by the identification of predicate devices, adopting methodology from Heneghan et al. (2017). The first study produced a device's family tree as traced through the FDA's 510(k) process. The results document that the process is broken in several specific ways, and needs to be fixed, as detailed in Chapter 2.

The second study of the dissertation was inspired by medico-legal precedent. This study examined the medical device manufacturing industry with respect to patient safety, patient well-being and acceptance of implanted devices. The intent was to develop an approach or tool to ascertain the relative risk and performance of a specific medical device in comparison to a category of medical devices. This proof-of-concept exercise focused on the safety of a specific surgical mesh device in comparison to the category of all mesh devices. The approach integrated entries of adverse events in the FDA's Total Product Lifecyle (TPLC) database with the established Association for the Advancement of Automotive Medicine's (AAAM's) Abbreviated Injury Scale (AIS).

Patient problems as recorded in the FDA's Total Product Lifecyle (TPLC) and Manufacturer and User Facility Device Experience (MAUDE) database were collected and evaluated for the FTL category of devices and Ethicon's PROCEED Ventral Patch Medium Mesh, respectively. This was conducted based upon the literature-based assumption that the more advanced the device innovation, the safer the device, as

measured by adverse events (AEs). It was expected that the more advanced the device innovation, the less impact to patient safety. And finally, it was expected that the worse the patient experience, the less safe the device.

In summary, the results of this second research project can be identified as:

1. Application of Abbreviated Injury Scale (AIS) for FDA's FTL product category of all surgical mesh medical device products (2021 – 2022)
2. Application of Abbreviated Injury Scale (AIS) for Ethicon PROCEED Ventral Patch (PVP) Medium (6.4 cm x 6.4 cm) singular surgical medical mesh device product (2021 – 2022)
3. Identification of the device performance of the Ethicon PVP surgical mesh as better than the category of mesh devices (2021 – 2022) in both quantity and quality
    a. Quantity: In the two years of data considered, while there were 100 different patient problems reported for FTL product category. There are 35 types of patient problems for Ethicon PVP Medium Mesh. There are no recorded deaths for Ethicon PVP Medium Mesh devices, there are 14 deaths in the full FTL category of mesh devices.
    b. Quality: Proportionately less problems reported with greater severity for Ethicon's PVP Medium Mesh in comparison to FTL product category of all mesh devices. Specifically, the data reports, 28% of patient problems in FTL product category are 3/Serious, 4/Severe, 5/Critical or 6/Maximal. Whereas only approximately 14% of patient problems for Ethicon PVP Medium Mesh are scaled as 3/Serious, 4/Severe, 5/Critical or 6/Maximal.

The overall contribution is that the proof of concept survived. There is a way to evaluate patient safety. The future applications are significant because the approach can begin to distinguish between manufacturers, brand names, materials and other device characteristics in terms of their performance and impact on patient safety.

There are limitations to this exercise. The first limitation is the disclaimer that any conclusions are made without the knowledge of the total universe of implanted devices. It is unknown how many devices were implanted over those two years, and it is unknown how many devices cause patient problems that were *not reported*. Our attempt to address this was to calculate all data as a percentage of total data available. It is important to remember that even this large and comprehensive data source is limited. This is the only data that is publicly available. While data on unreported problems would be highly desirable, especially in the context of litigation, the data used in the dissertation is the very data the FDA scrutinizes to issue recalls and cease distribution notices. The FDA data is highly meaningful. The FDA notes that the Manufacturer and User Facility Device Experience (MAUDE) database *should contribute to the cost-benefit assessment of devices.*

Another limitation is that the analysis focused upon just two years of data in one product category and on two years of data for a single mesh device within that category. The single device evaluated represented just 1% of all devices in that category for the two years. What is a directional indicator for one device over two years may not hold true for subsequent years. However, this is the most current information available and it has been evaluated in its entirety. The narrow scope of the investigation was appropriate for the

proof-of-concept objective. It lends itself to replication for a wide range of medical devices and time frames.

A broader concern is the difficulty of quantifying patient injury. The AIS scale is widely used, but it cannot capture all aspects of patient welfare. Some might argue there are nuances to medical device injuries that suggest special consideration outside of established scales. Jennett (1976) argued this position with respect to head/brain injuries. However, in the context of surgical mesh, the application of the AIS scale was a good fit. There is no obvious opportunity way to improve or expand the scale within the limitations of the proof of context exercise.

Despite these limitations, we can state with confidence that this proof-of-concept research exercise demonstrated value and promise. A recommendation to expand to other device categories and products can be made, to develop insights on product safety across a wide range of medical devices.

The research provides a starting point for future applications. Future applications could also consider manufacturers or materials. There is also the potential to convert the scaled values into an injury severity score. This is regularly applied in medical trauma literature. Potential scores range from 1 – 75. (Reynolds et al, 2011). [ISS = (AIS body region 1) ^{2} + (AIS body region 2) ^{2} + (AIS body region 3) ^{2}. Regions are head, thorax, extremity regions, respectively.] Details in MAUDE could support this. This would facilitate statistical comparisons. More sophisticated economic quantification of cost-benefits could also be explored, particularly after the scale is converted to a score. Statistical significance of severity scores for different devices could be determined. Opportunities to automate the data collection and coding should also be investigated,

using ChatGPT or other tools relying on artificial intelligence. In totality the dissertation research suggests there is potential for practical application, namely that *individual devices* can be evaluated against the *family of available devices* per adverse events recorded in the FDA's Manufacturer and User Facility Device Experience (MAUDE) database for their relative risk. The intent is to determine if the promise of medical device innovation, to improve or provide significant positive change in the life of a patient is being fulfilled.

Rectifying the Medical Device Marketplace

From a practitioner's point of view, there is much work to be done. There are multiple stakeholders involved, as this complicated problem demands a multi-pronged approach. Reform needs to come for the FDA's 510(k) approval process. The ramifications of this faulty process are well-documented.

In 2011, the Institute of Medicine (IOM) conducted a review of FDA device approval processes. IOM's primary criticism was that the clearance process did not include an evaluation, either premarket or post-market, of the product's safety (IOM, 2011). In cases in which the product is truly a clone of a currently marketed device, substantial equivalency is not necessarily an incorrect standard (IOM, 2011). However, substantial equivalence does not guarantee that the device poses the same risks and performs similarly to an older device, particularly when the device is a chimera of multiple predicates (IOM, 2011). And the manufacturer can use as a predicate an old, discontinued device or a device that was approved, but never marketed (Committee on the Public Health Effectiveness of FDA's 510(k) Clearance Process, 2011). That same year, Public Citizen concluded the 510(k) approval process favors the medical industry

and puts consumers at risk (Wolfe, 2011). Essentially, most medical devices have never been tested for safety (Consumer Reports, 2012). The human consequences of the faulted FDA's 510(k) approval process are sobering.

Device failure (or worse) stories are plentiful (see Table 15). Allen (2013) reported that for 2007, medical interventions (including medical device implantation) were the third leading cause of death in the United States (behind heart disease and cancer), killing an estimated 210,000 to 440,000 Americans. In 2015, approximately 16,000 deaths associated with medical devices were reported to the FDA (Lenzer, 2017, p. 61). An analysis from the General Accountability Office (GAO) found that 99% of device-related adverse events are never reported to the FDA, and the more serious the event, the less likely it is to be reported (Chelimsky, 1986). That means medical devices could have been associated with as many as 1.6 million deaths in 2015 (Lenzer, 2017, p. 61). Even if only 1% - 10% of those deaths were caused by a device, that means between 16,000 and 160,000 people may have been killed by devices, making medical devices [again] one of the leading causes of death in the United States (Lenzer, 2017, p. 61). Medical device industry is one of the most powerful yet unaccountable sectors of the medical-industrial complex (Lenzer, 2017, p. 67).

Table 15: Examples of Medical Device Failures

Source: Various

Allergan's Lap-bands Lap-bands were approved based upon a lone study of 299 people, in which 51% reported chronic nausea or vomiting or both and 25% had their bands removed before the end of the three-year study because of complications or failure to lose enough weight (Consumer Reports, 2012). FDA recall posted in 2010.
Cyberonics' Aspire Seizure Response Vagus Nerve Stimulator (VNS) Therapy Engineered to provide electrical stimulation to a patient's vagus nerve to manage seizures. Operational failures impacted battery life and resulted in failure to the point where the device induced the very conditions and symptoms it was designed to treat (Miller, 2018, Lenzer, 2017). Series of FDA recalls posted 2015, 2017 and 2018.
Boston Scientific's ProteGen Sling Collagen A transvaginal surgical mesh (TVM) product. Categorized as Class II device, TVM went to the market with 510(k) approval, exercising the substantial equivalency regulatory guideline, tied to a predicate device given prior approval (Shobeiri, 2019) (Consumer Reports, 2011). TVM was used to assist patients experiencing medical issues from a prolapsed uterus and/or bladder (Shobeiri, 2019). The mesh can become contaminated and erode, while it resides in an organ-rich space in the body creating numerous complications compromising a patient's quality of life (Consumer Reports, 2011). Often, their only recourse has been litigation – some estimate 3,000 cases have been adjudicated to-date, with more than 25,000 pending (Andrus Wagstaff, n.d.) FDA recall posted in 1999.
Johnson & Johnson's Pinnacle Hip Implant Medical debris escaping from cobalt metal hip joints has been found to cause slow and profound poisoning, where recipients' mental health deteriorated to the point of induced psychotic episodes (Ziering et al., 2018). FDA recall posted in 2013.
Draeger Medical Breathing and Anesthesia Set VentStar: Distributed beginning April 2016 with FDA approval, this device provides mechanical ventilation and critical breathing support to patients (Pulmonology Advisor, 2019) (Ausick, 2019). The devices may have been incorrectly assembled resulting in a short-circuit in the breathing hose that may lead to irreversible patient harm, up to and including death (Ausick, 2019). Recalled January 25, 2019.

Change is possible. However, it requires the dedicated work of various stakeholders (see Figure 29). Numerous practical suggestions emerge from the research findings for the stakeholders, including: the regulatory agency; providers; patients and partners; insurers; medical device manufacturing companies; academy and institutions;

and policy makers. For each of these stakeholders, a few suggestions can be detailed as a starting point as follows:

Regulatory Agency: This means you, FDA! Facilitate accountability. Apply more rigor to the approval process, be more discriminatory in assessment of low, medium and high-risk device classifications. Offer multiple reviews in an attempt for more scrutiny of all and nay clinical evidence. Be especially sensitive to emerging technologies. (Therapeutic Goods Association, 2023).

Providers: Influence. Challenge suppliers; request clinical data and resources. Generate consumer awareness. Share information with patients. Have authentic and candid consultations with patients. Encourage second opinions. Surgery is serious and often should be the final option of care.

Patients & Partners: Advocate. Be aware. Seek second (and third) opinions. A surgeon gets paid to perform surgery. But for the patient, it should be an option of last resort. Ask how to report and address patient problems. Ask about the relative injury risk of the suggested device compared to the product category as a whole. Ask about patient experiences 5 to 10 years after device implantation.

Insurers: Discriminate. All medical devices are not the same. Request evidence of relative safety. Reward safety and efficacy. Exercise value analysis teams. Consider payor caps on less-proven devices.

Medical Device Manufacturing Companies: Innovate. Establish and host expert groups with consumer representation. Make it easier to report adverse events and patient problems. Identify in-house resources and strategic partners to collect data and complete and share analyses. The known is always more manageable than the unknown. Reap the benefits of brand recognition for being a leader in your device space.

Academy & Institutions: Investigate. Academics and institutions like think tanks, do what you do best. FDA data is public. Identify research partners in the device manufacturing field. Effect change. As Porter (1995) would remind us, quantitative rigor can be fueled by social and political pressures and can have significant contributions at the intersection of culture, science, and bureaucracy.

Policymakers: Establish standards. Revisit and update earlier General Accounting Office and Institute of Medicine studies in this space to inform immediate minor adjustments now and staged, more significant policy changes for the future. Patient safety needs to be explicit in the approval process. Increase transparency of relative product safety, and long-term consequences of implanted medical devices. Quantifying and reducing risk in medical device implantation experience benefits everyone. This is important to ensure the United States' continued global dominance in health care. Projected long-term benefits of recommended improvements should be completed.

With each of the stakeholders utilizing their expertise within their respective fields to effect change, they will bring forth a burst of sunshine upon the medical device marketplace. Past shortcomings can be rectified, and future crises can be avoided. Meanwhile, as a reminder, the patient is always the last line of defense. Patient consent must be granted before any major medical procedure. Patients should not be afraid to ask direct questions of surgeons before providing written consent. To facilitate that conversation, see the checklist developed from the research findings: *Seven to Survive and Thrive* (see Figure 30). By advocating for themselves and not assuming all medical devices will be safe for them, patients and their families can help to drive meaningful and positive change within the medical device sector.

Figures

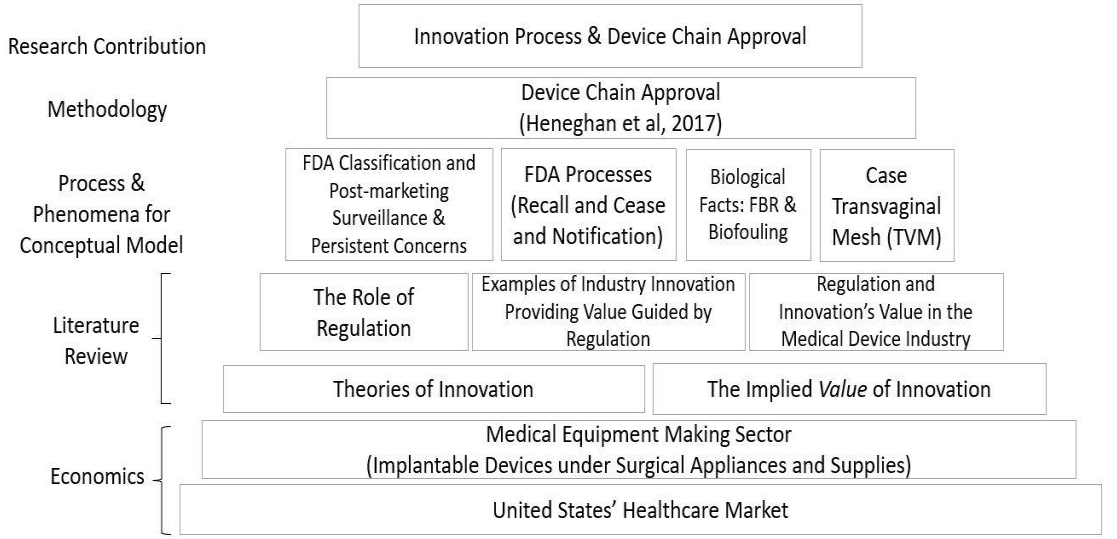


Figure 1: Research Scaffolding Part I

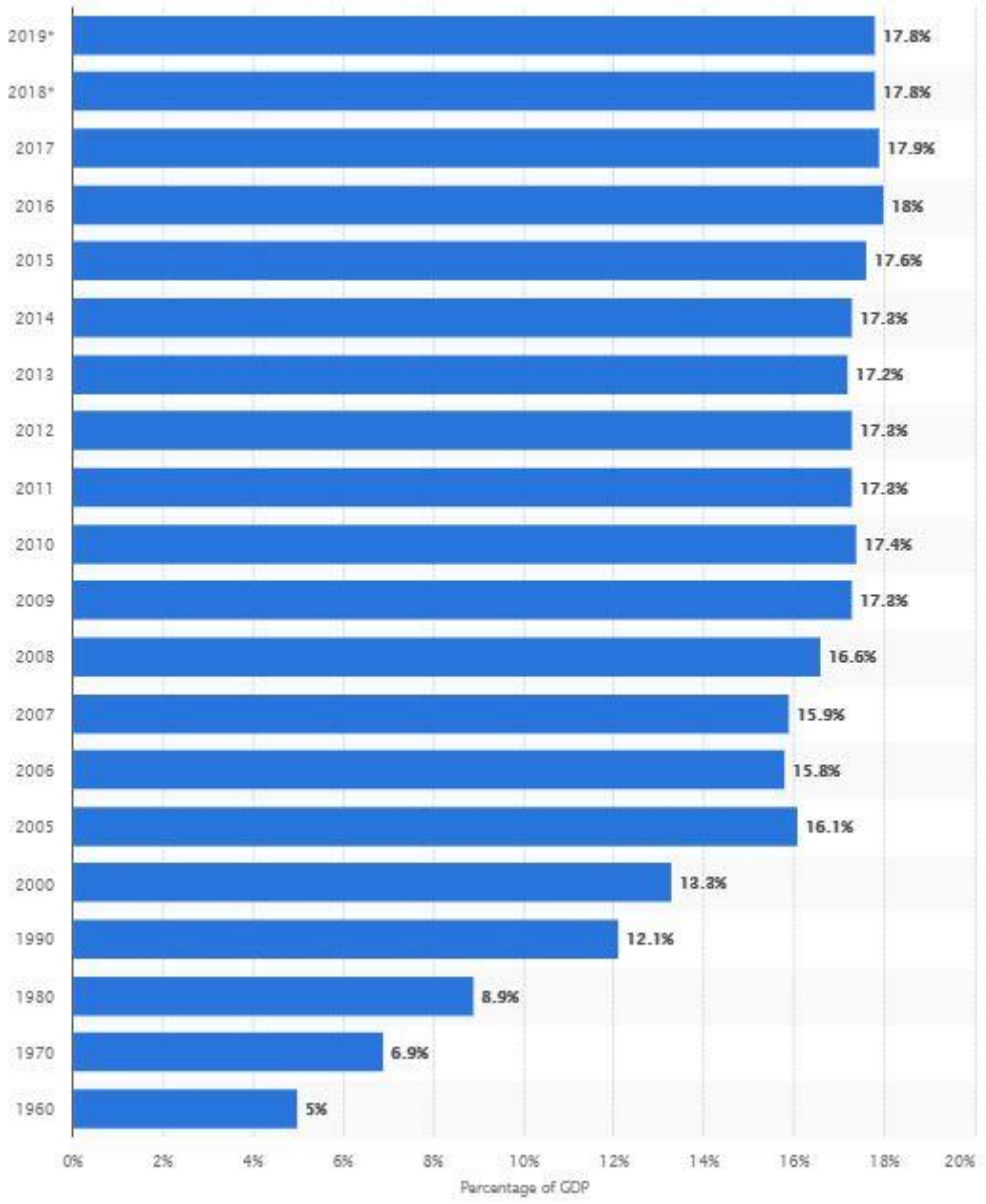


Figure 2: U.S. National Health Expenditures as Percent of GDP from 1960 to 2019

(Statistica, n.d.)

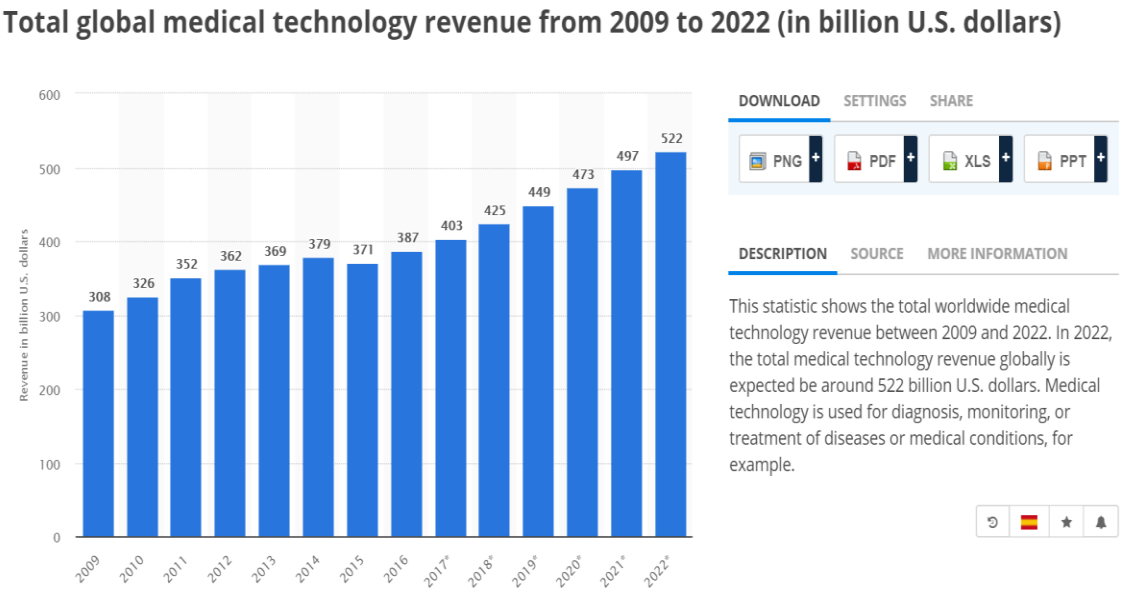


Figure 3: Total Global Medical Technology Revenue from 2009 – 2022

(Statistica, n.d.)

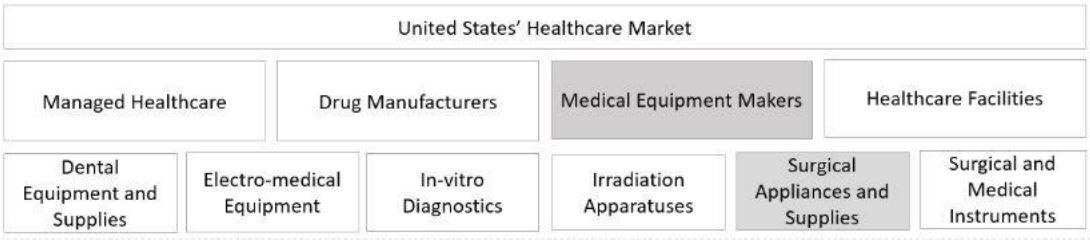


Figure 4: United States' Healthcare Market

(Deutsch, 2019)

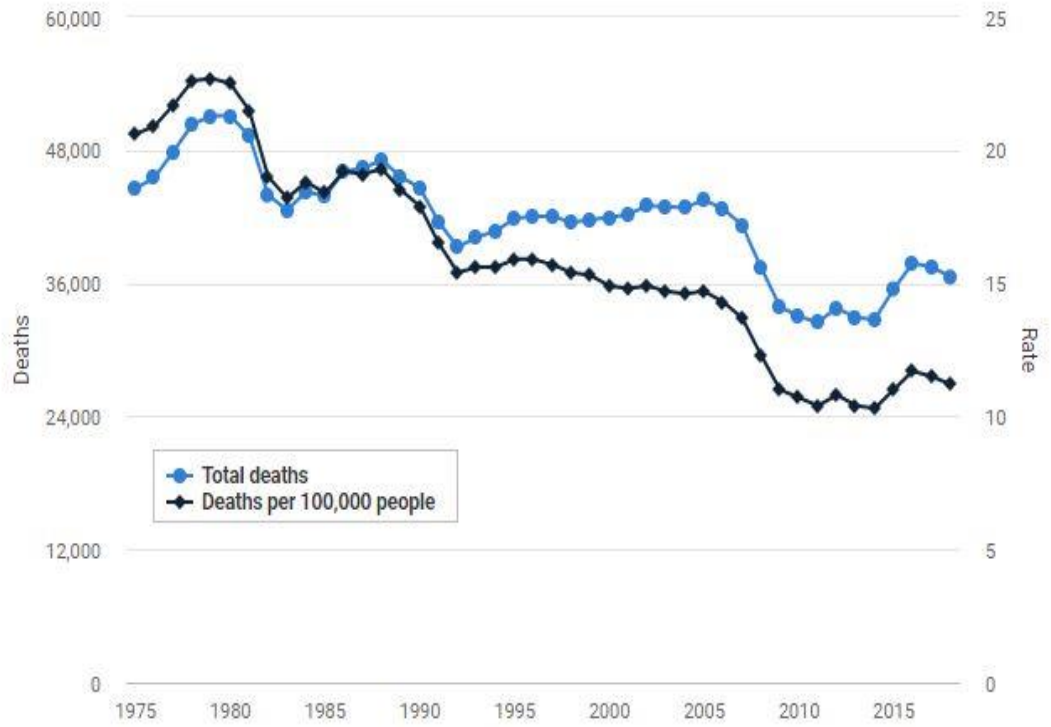
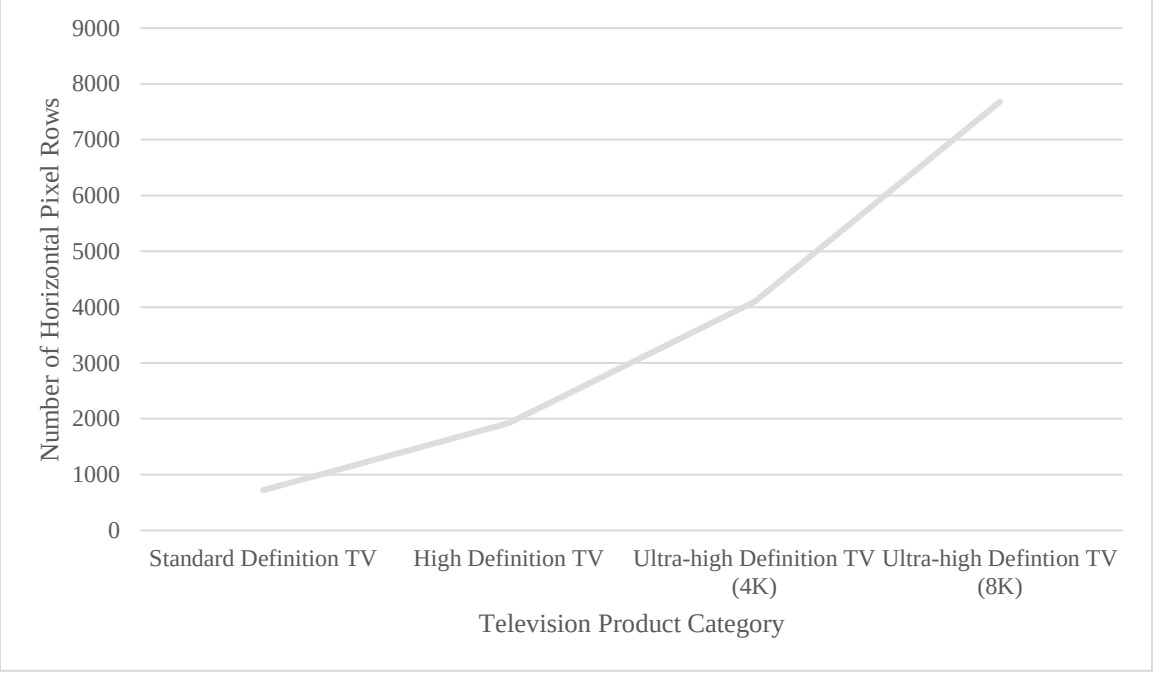


Figure 5: Motor Vehicle Crash Deaths and Deaths per 100,000 People 1975 – 2018

[NHTSA Fatality Analysis Reporting System (FARS)]



Television Product Category	Standard Definition Television	High Definition (HD) Television	4K Ultra-High Definition (UHD)Television	8K Ultra-high Definition (UHD)Television
Screen Resolution (Pixels)	720 x 480	1920 x 1080	4096 x 2160	7680 x 4320
Pixels per Frame	345K	2.1M	8.8M	33M
Megapixels Transmitted per Second	10.4	124	531	1,991
Required Bandwidth for Video Signal in Billions of Bits per Second (Gbps)	.25	3	16	60

Figure 6: Trend in Television Screen Resolution Quality

(Shalinksy, 2016)

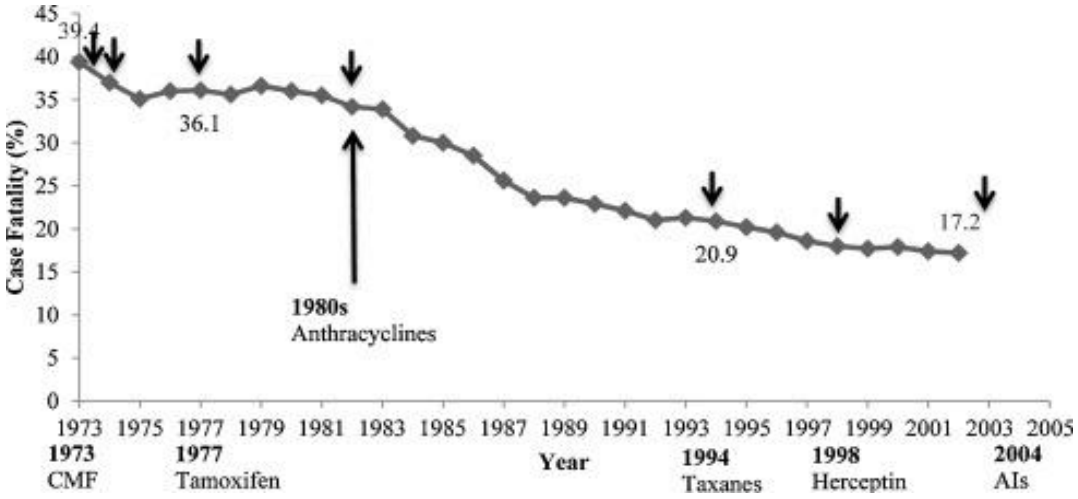


Figure 7: Ten-Year Breast Cancer Case Fatality and Historical Timeline of Breast Cancer Chemotherapy

(Narod et al, 2015)

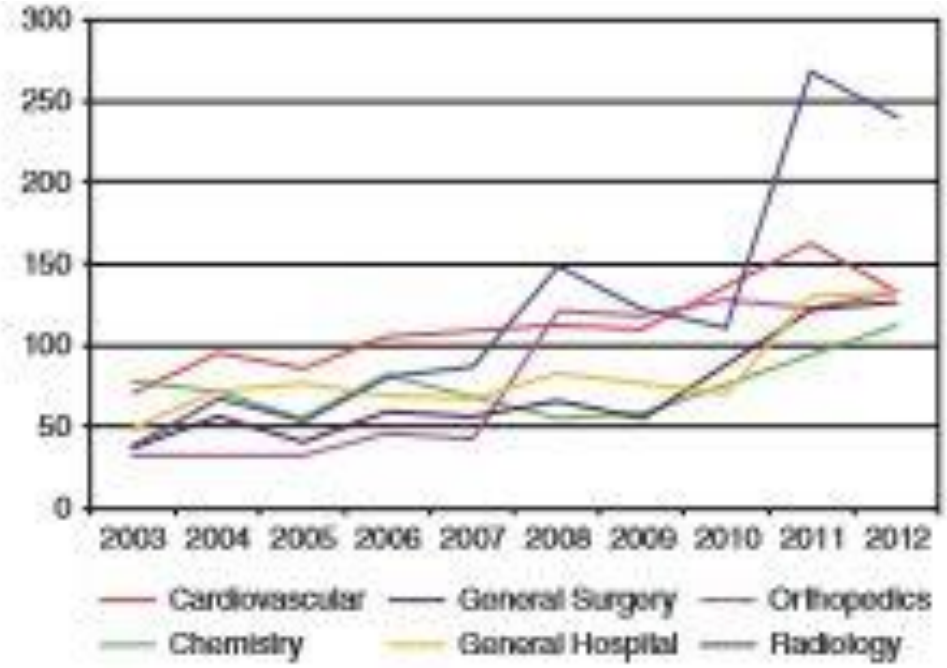


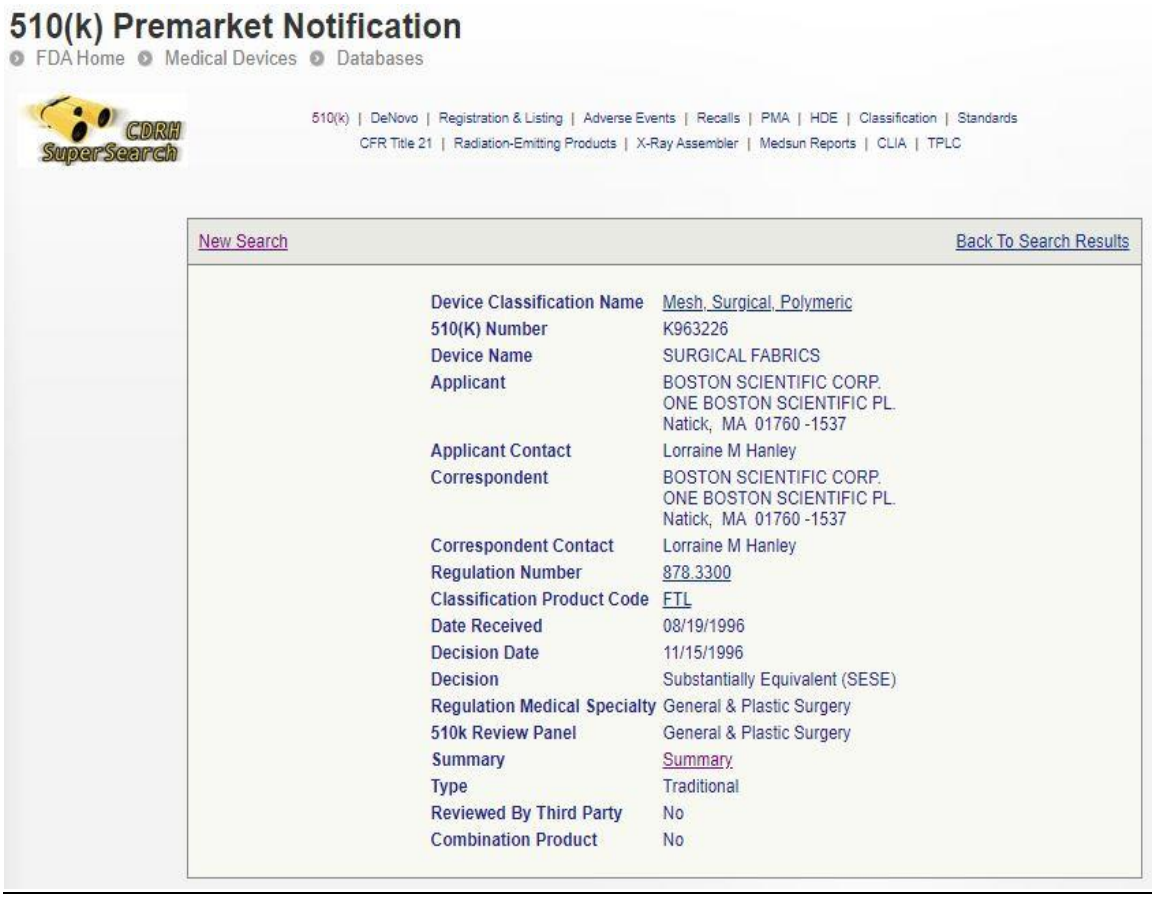
Figure 8: Trend in Device Recalls by Medical Specialty 2003 – 2012

(FDA, n.d.)

COMPANY	PENDING ACTIONS	TOTAL ACTIONS
C.R. Bard	16	15,868
American Medical Systems	80	21,367
Boston Scientific	965	26,617
Ethicon	1,202	40,761

Figure 9: Transvaginal Mesh (TVM) Cases as of November 2019

(Drugwatch, n.d.; Unites States Judicial Panel on Multidistrict Litigation, 2019)



510(k) Premarket Notification

FDA Home | Medical Devices | Databases

CDRH SuperSearch

510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

New Search | Back To Search Results

Device Classification Name	Mesh, Surgical, Polymeric
510(K) Number	K963226
Device Name	SURGICAL FABRICS
Applicant	BOSTON SCIENTIFIC CORP. ONE BOSTON SCIENTIFIC PL. Natick, MA 01760 -1537
Applicant Contact	Lorraine M Hanley
Correspondent	BOSTON SCIENTIFIC CORP. ONE BOSTON SCIENTIFIC PL. Natick, MA 01760 -1537
Correspondent Contact	Lorraine M Hanley
Regulation Number	878.3300
Classification Product Code	FTL
Date Received	08/19/1996
Decision Date	11/15/1996
Decision	Substantially Equivalent (SESE)
Regulation Medical Specialty	General & Plastic Surgery
510k Review Panel	General & Plastic Surgery
Summary	Summary
Type	Traditional
Reviewed By Third Party	No
Combination Product	No

Figure 10: 510(k) Premarket Notification Search Results Page - Boston Scientific's ProteGen Sling K963226

(FDA, 2020)

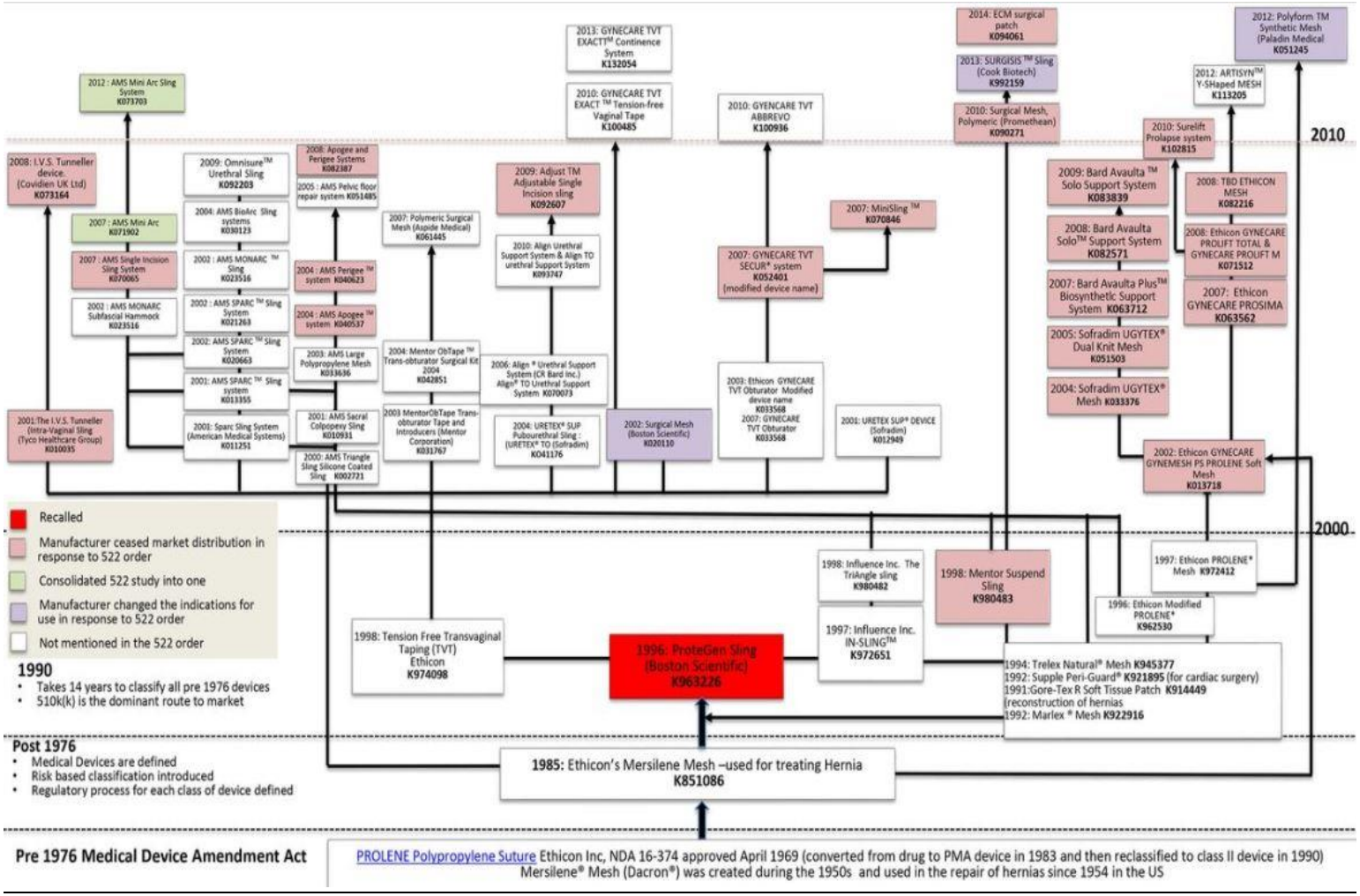
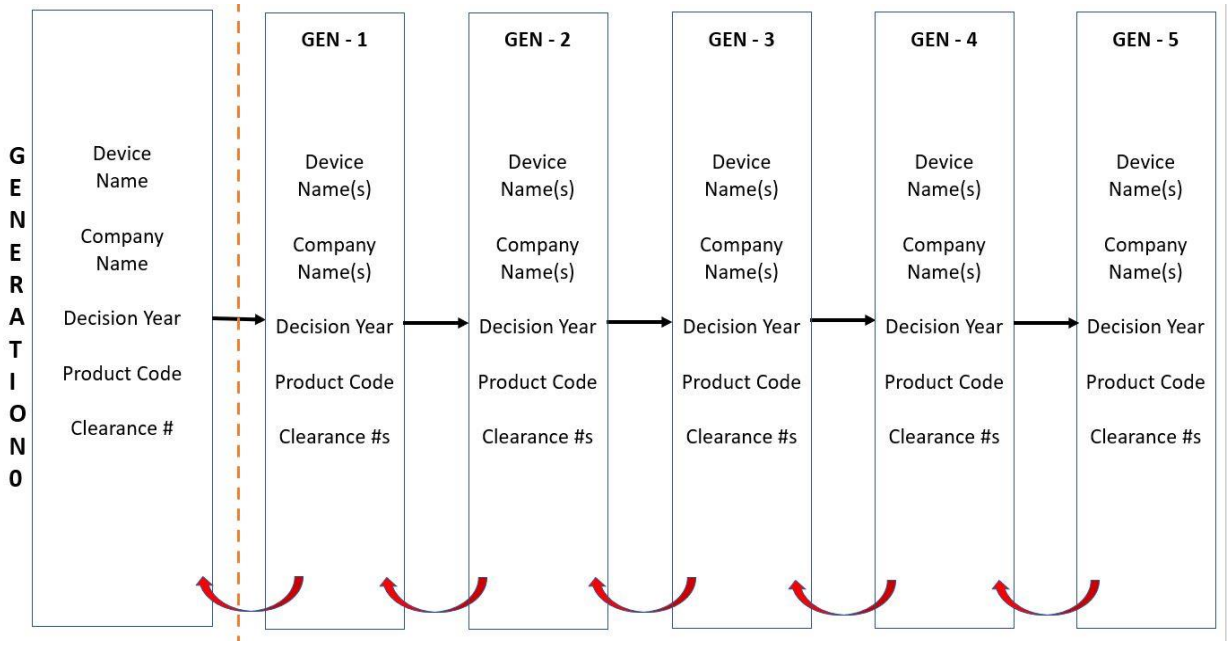


Figure 11: Food and Drug Administration Device Chain Approval for Transvaginal Mesh

https://bmjopen.bmj.com/content/bmjopen/7/12/e017125/F1.large.jp



Indicates sequence of innovation, timeline.

Indicates predicate device relationship.

Generation 0 is ascribed to our starting device. Each predicate device is ascribed a minus generation number of -1 through -5 depending upon how many 'links in the chain' exist between the current predicate device and our original device.

Generation columns will be populated based upon public information available in FDA's 510(k) database.

Figure 12: Conceptual Model: Medical Device Chain of Innovation - Generational View

CDRH SuperSearch

510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

New Search | Back To Search Results

Device Classification Name	Mesh, Surgical
510(K) Number	K141053
FOIA Releasable 510(K)	K141053
Device Name	OVINE TISSUE MATRIX(OTM)
Applicant	TELA BIO, INC. 1 GREAT VALLEY PARKWAY, SUITE 24 Malven, PA 19355
Applicant Contact	Donna Stauffer
Correspondent	TELA BIO, INC. 1 GREAT VALLEY PARKWAY, SUITE 24 Malven, PA 19355
Correspondent Contact	Donna Stauffer
Regulation Number	878.3300
Classification Product Code	FTM
Date Received	04/24/2014
Decision Date	12/11/2014
Decision	Substantially Equivalent (SESE)
Regulation Medical Specialty	General & Plastic Surgery
510k Review Panel	General & Plastic Surgery
Summary	Summary
Type	Traditional
Reviewed By Third Party	No
Combination Product	No

TELA BIO SURGICAL RECONSTRUCTION COMPANY

510(k) Number: k141053

Page 2 of 3

Summary of Technological Characteristics:

Device	Ovine Tissue Matrix	Endoform Reconstructive Template
Manufacturer	TELA Bio, Inc.	Mesynthes, Ltd.
510(k) Number	Proposed	K130547
Indications for Use	Ovine Tissue Matrix is intended for use as a surgical mesh to reinforce and/or repair soft tissue where weakness exists. Indications for use include the repair of hernias and/or body wall defects that require the use of reinforcing or bridging material to obtain the desired surgical outcome.	Endoform Reconstructive Template is intended for use as a surgical mesh to reinforce and/or repair soft tissue where weakness exists. Indications for use include, but are not limited to, the following procedures: hernioplasty and repair of body wall defects. The device allows reinforcement or bridging of a deficit to obtain the desired surgical outcome.
Material	Ovine derived collagen and associated ECM components Collagen I Collagen III Polypropylene	Ovine derived collagen and associated ECM components Collagen I Collagen III Polyglycolic acid (PGA)
Design	Terminally sterilized	Terminally sterilized
Dimensions	Various sizes, up to 1000 cm^2	Various sizes, up to 200 cm^2
Thickness	Approx. 0.15-1.2 mm	Approx. 0.15-1.2 mm

Figure 13: 510(k) Premarket Notification Search Results Page and Summary Excerpt with Predicate Device - TELA Bio's Ovine Tissue Matrix (OTM) (K141053)

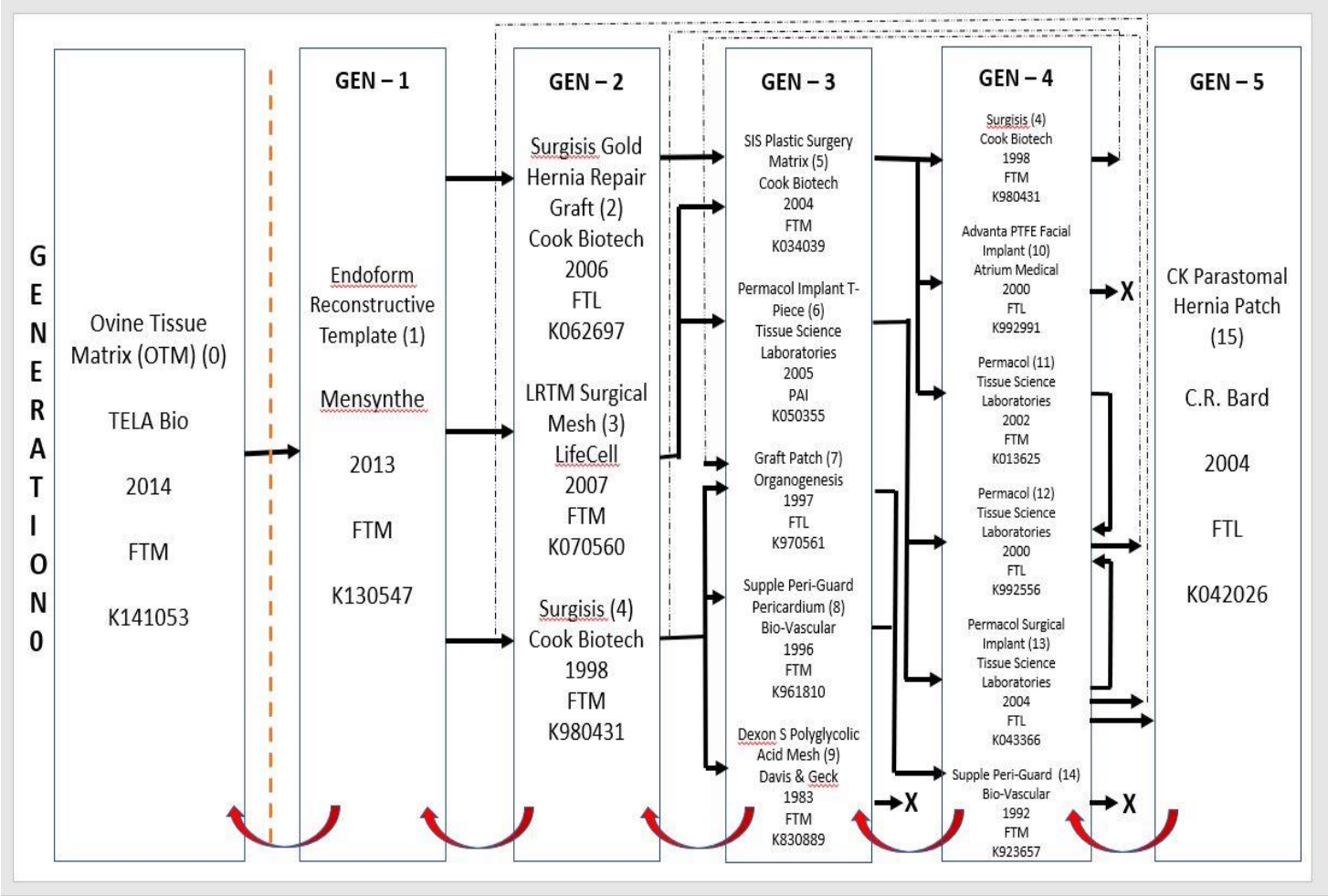
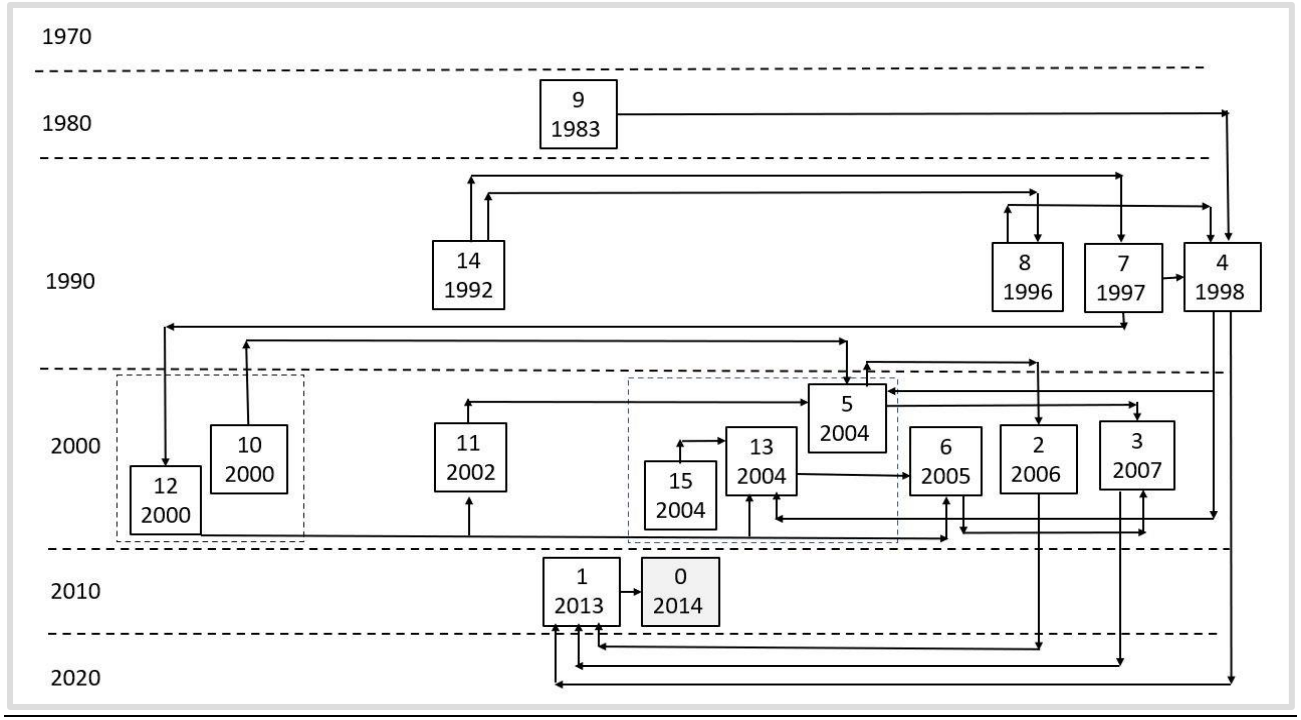


Figure 14: A Medical Device Family Tree: TELA Bios' Ovine Tissue Matrix (OTM) Chain of Substantially Equivalent Devices - Generational View

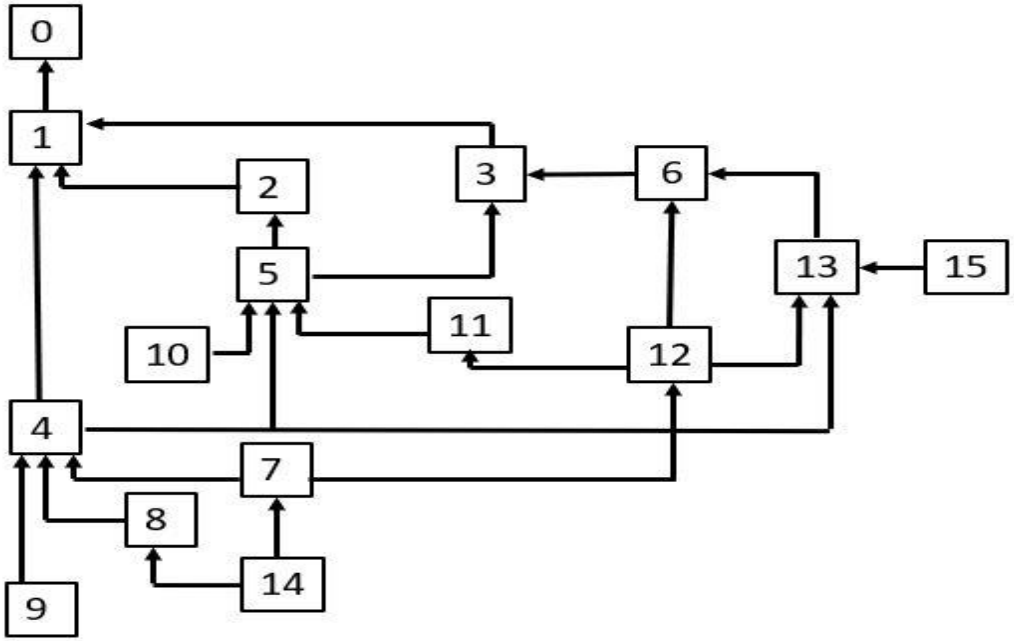
(Pharm3R, 2019; 510(k), 2019)



0 – Ovine Tissue Matrix (OTM), TELA Bio, 2014, FTM, K141053
1 –Endoform Reconstructive Template, Mensynthe, 2013, FTM, K130547
2 – Surgisis Gold Hernia Repair Graft, Cook Biotech, 2006, FTL, K062697
3 – LRTM Surgical Mesh, LifeCell, 2007, FTM, K070560
4 – Surgisis, Cook Biotech, 1998, FTM, K980431
5 – SIS Plastic Surgery Matrix, Cook Biotech, 2004, FTM, K034039
6 – Permacol Implant T-Piece, Tissue Science Laboratories, 2005, PAI, K050355
7 – Graft Patch, Organogenesis, 1997, FTL, K970561
8 – Supple Peri-Guard Pericardium, Bio-Vascular, 1996, FTM, K961810
9 – Dexon S Polyglygolic Acid Mesh, Davis & Geck, 1983, FTM, K830889
10 – Advanta PTFE Facial Implant, Atrium Medical, 2000, FTL, K992991
11 – Permacol, Tissue Science Laboratories, 2002, FTM, K013625
12 – Permacol, Tissue Science Laboratories, 2000, FTL, K992556
13 – Permacol Surgical Implant, Tissue Science Laboratories, 2004, FTL, K043366
14 – Supple Peri-Guard, Bio-Vascular, 1992, FTM, K923657
15 – CK Parastomal Hernia Patch, C.R. Bard, 2004, FTL, K042026

Figure 15:A Medical Device Family Tree: TELA Bio's Ovine Tissue Matrix (OTM) Chain of Substantially Equivalent Devices - Temporal View By Decade

(Pharm3R, 2019; 510(k), 2019)



0 – Ovine Tissue Matrix (OTM), TELA Bio, 2014, FTM, K141053
1 –Endoform Reconstructive Template, Mensynthe, 2013, FTM, K130547
2 – Surgisis Gold Hernia Repair Graft, Cook Biotech, 2006, FTL, K062697
3 – LRTM Surgical Mesh, LifeCell, 2007, FTM, K070560
4 – Surgisis, Cook Biotech, 1998, FTM, K980431
5 – SIS Plastic Surgery Matrix, Cook Biotech, 2004, FTM, K034039
6 – Permacol Implant T-Piece, Tissue Science Laboratories, 2005, PAI, K050355
7 – Graft Patch, Organogenesis, 1997, FTL, K970561
8 – Supple Peri-Guard Pericardium, Bio-Vascular, 1996, FTM, K961810
9 – Dexon S Polyglygolic Acid Mesh, Davis & Geck, 1983, FTM, K830889
10 – Advanta PTFE Facial Implant, Atrium Medical, 2000, FTL, K992991
11 – Permacol, Tissue Science Laboratories, 2002, FTM, K013625
12 – Permacol, Tissue Science Laboratories, 2000, FTL, K992556
13 – Permacol Surgical Implant, Tissue Science Laboratories, 2004, FTL, K043366
14 – Supple Peri-Guard, Bio-Vascular, 1992, FTM, K923657
15 – CK Parastomal Hernia Patch, C.R. Bard, 2004, FTL, K042026

Figure 16: Another Schematic View of the Medical Device Family Tree of Substantially Equivalent Devices for TELA Bio Ovine Tissue Matrix (OTM)

(Pharm3R, 2019; 510(k), 2019

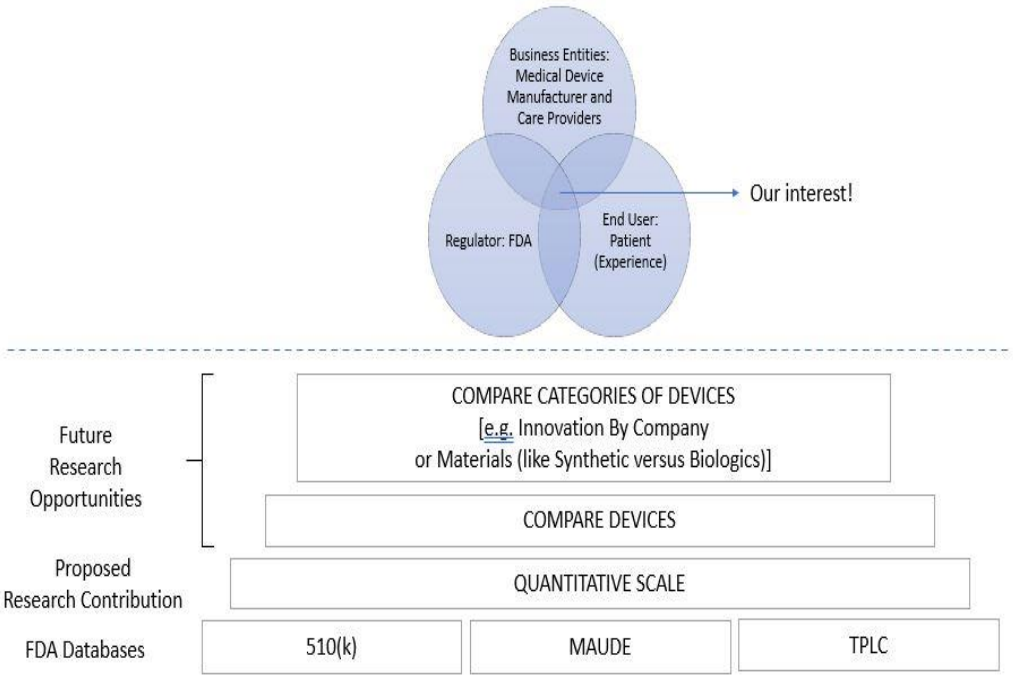
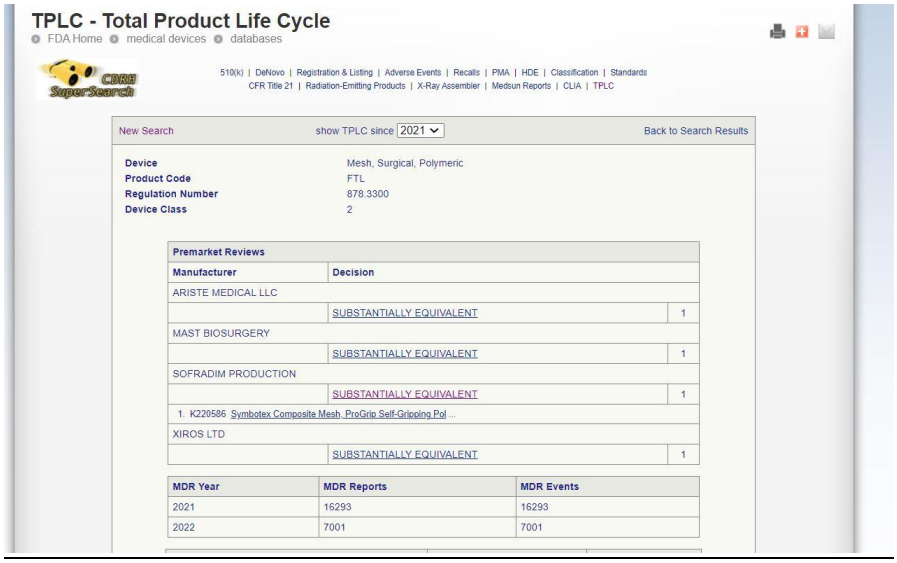


Figure 17: Research Scaffolding Part II



Scar Tissue	1255	1255
Emotional Changes	984	984
Discomfort	894	894
Nausea	891	891
Obstruction/Occlusion	856	856
Abscess	730	730
Decreased Appetite	670	670
Abdominal Pain	614	614
Diarrhea	607	607
Chills	601	601
Disability	593	593
Seroma	547	547
Weight Changes	516	516
Erosion	461	461
Fistula	377	377
Swelling/ Edema	323	323

Figure 18:FDA's Total Product Life Cycle (TPLC) Sequenced Screen Shots

Relative scale of patient experience via recorded adverse events.

The lower the score, the better a patient's quality-of-life.

Figure 19: FDA's Medical Device Safety

Figure 20: Adverse Events by Frequency

Category	Weight	Frequency	Percentage Calculation
A	1		
B	2		
C	3		
D	4		
E	5		
F	6		

Sum of Categories (Weight x Frequency) = Product Category Score (1 – 6)

Figure 21: Application Association for Advancement of Automotive Medicine (AAAM's) Abbreviated Injury Scale (AIS)

(Franklyn & Lee, 2017, Chapter 4; Baker et al., 1974)

Sample Category	Patient Experience Impact upon Patient Quality-of-Life	Examples
A	Minor	Scarring
B	Moderate	Constipation
C	Serious	Bacterial Infection
D	Severe	Bowel Perforation
E	Critical	Sepsis
F	Maximal	Death

Figure 22: Sample Descriptions

(Franklyn & Lee, 2017, Chapter 4; Baker et al., 1974; Association for the Advancement of Automotive Medicine, 2015, p xv)

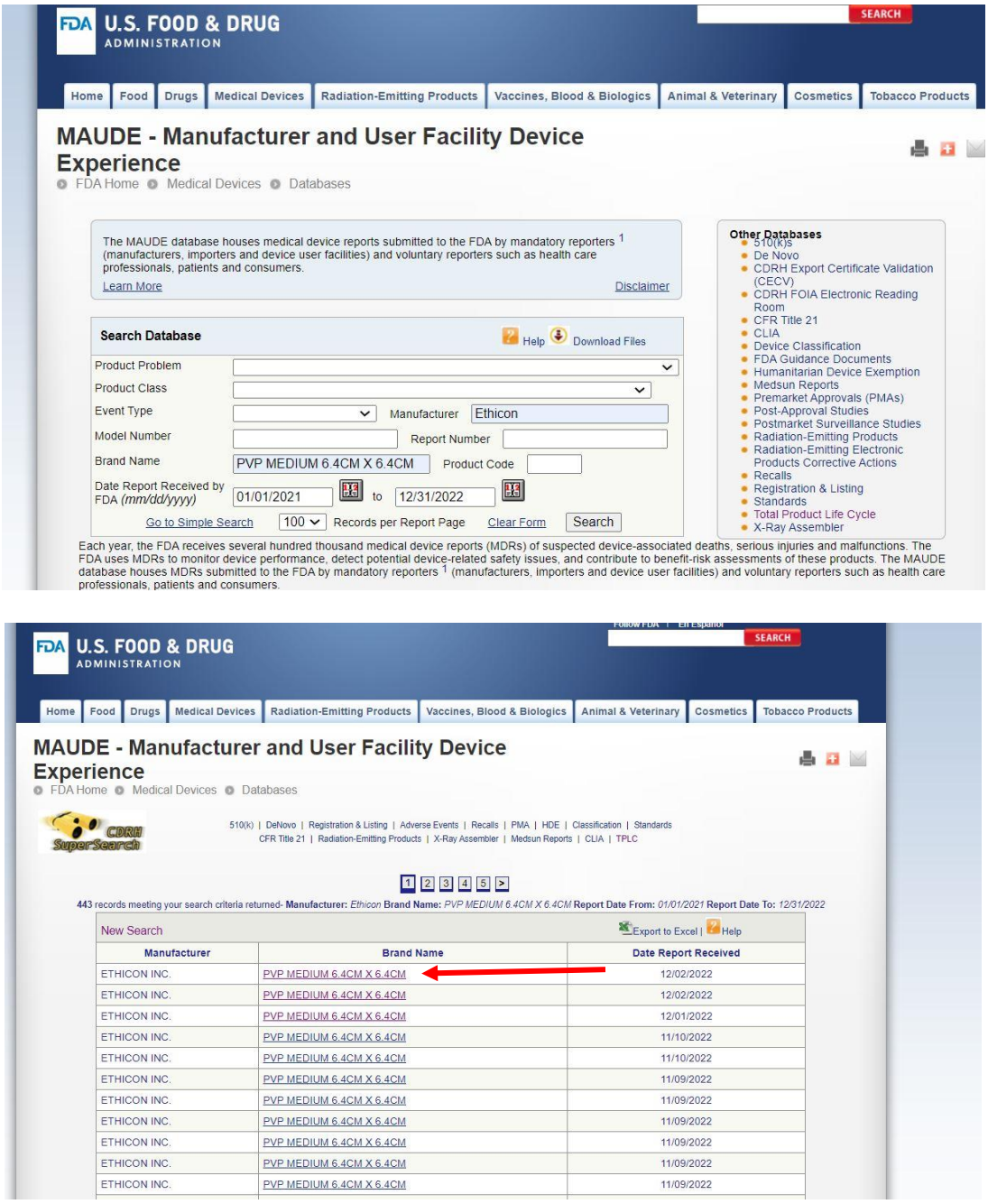
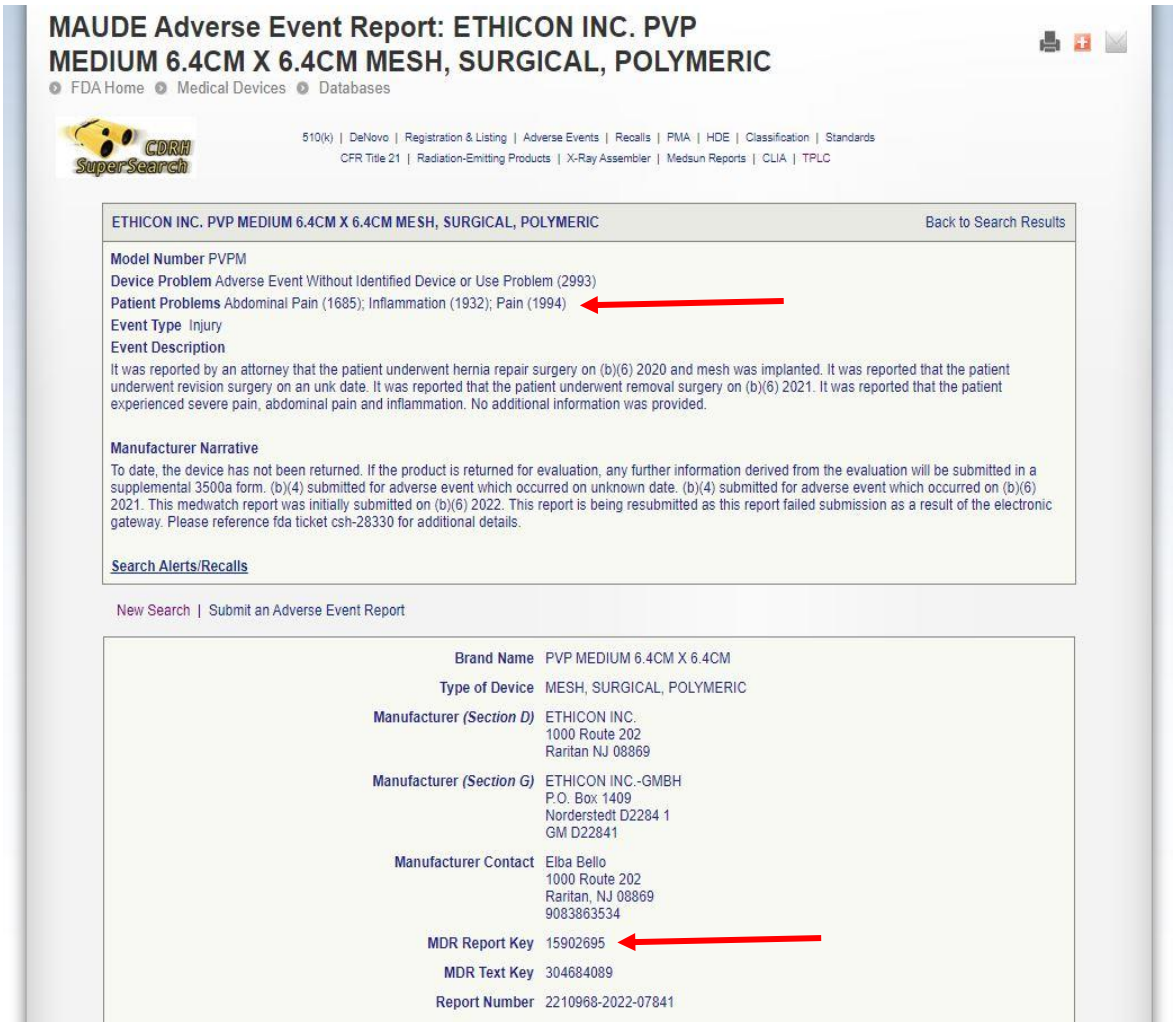


Figure 23: FDA's Manufacturer and User Facility Device Experience (MAUDE) Database Search, Results and Records - Ethicon PVP Medium 6.5 cm x 6.5 cm Mesh – Screenshots

(FDA's Manufacturers and User Facility Device Experience (MAUDE) Database)



MAUDE Adverse Event Report: ETHICON INC. PVP MEDIUM 6.4CM X 6.4CM MESH, SURGICAL, POLYMERIC

FDA Home | Medical Devices | Databases

510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

ETHICON INC. PVP MEDIUM 6.4CM X 6.4CM MESH, SURGICAL, POLYMERIC — Back to Search Results

Model Number PVPM
Device Problem Adverse Event Without Identified Device or Use Problem (2993)
Patient Problems Abdominal Pain (1685); Inflammation (1932); Pain (1994)
Event Type Injury
Event Description
It was reported by an attorney that the patient underwent hernia repair surgery on (b)(6) 2020 and mesh was implanted. It was reported that the patient underwent revision surgery on an unk date. It was reported that the patient underwent removal surgery on (b)(6) 2021. It was reported that the patient experienced severe pain, abdominal pain and inflammation. No additional information was provided.

Manufacturer Narrative
To date, the device has not been returned. If the product is returned for evaluation, any further information derived from the evaluation will be submitted in a supplemental 3500a form. (b)(4) submitted for adverse event which occurred on unknown date. (b)(4) submitted for adverse event which occurred on (b)(6) 2021. This medwatch report was initially submitted on (b)(6) 2022. This report is being resubmitted as this report failed submission as a result of the electronic gateway. Please reference fda ticket csh-28330 for additional details.

Search Alerts/Recalls

New Search | Submit an Adverse Event Report

Brand Name	PVP MEDIUM 6.4CM X 6.4CM
Type of Device	MESH, SURGICAL, POLYMERIC
Manufacturer *(Section D)*	ETHICON INC. 1000 Route 202 Raritan NJ 08869
Manufacturer *(Section G)*	ETHICON INC.-GMBH P.O. Box 1409 Norderstedt D2284 1 GM D22841
Manufacturer Contact	Elba Bello 1000 Route 202 Raritan, NJ 08869 9083863534
MDR Report Key	15902695
MDR Text Key	304684089
Report Number	2210968-2022-07841

Figure 23: FDA's Manufacturer and User Facility Device Experience (MAUDE) Database Search, Results and Records – Ethicon PVP Medium 6.4 cm x 6.4 cm Mesh – Screenshots (Continued)

(FDA's Manufacturer and User Facility Device Experience (MAUDE) Database)

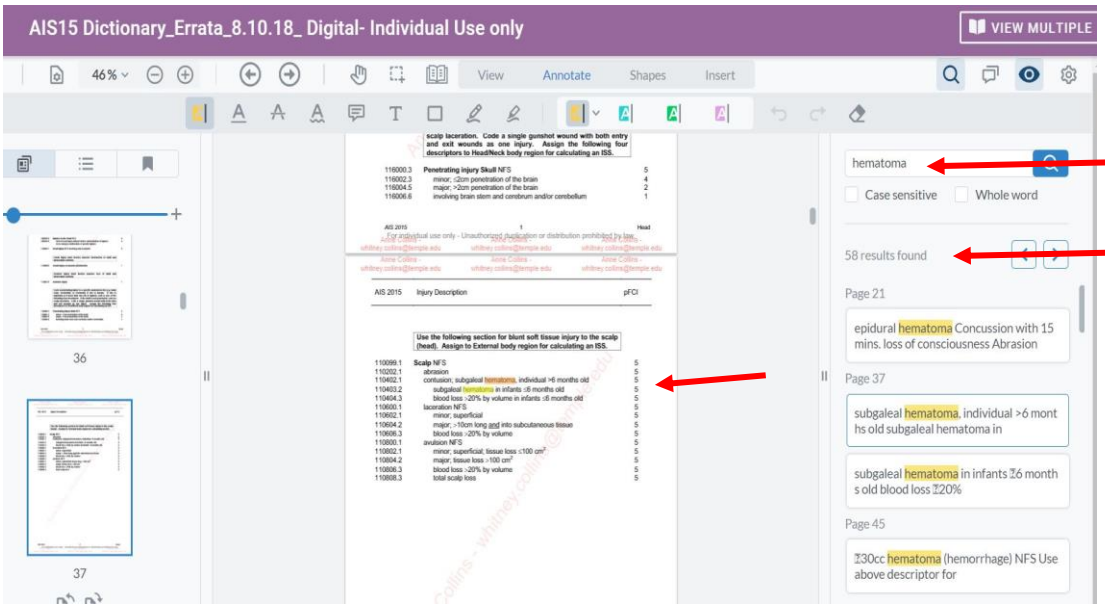
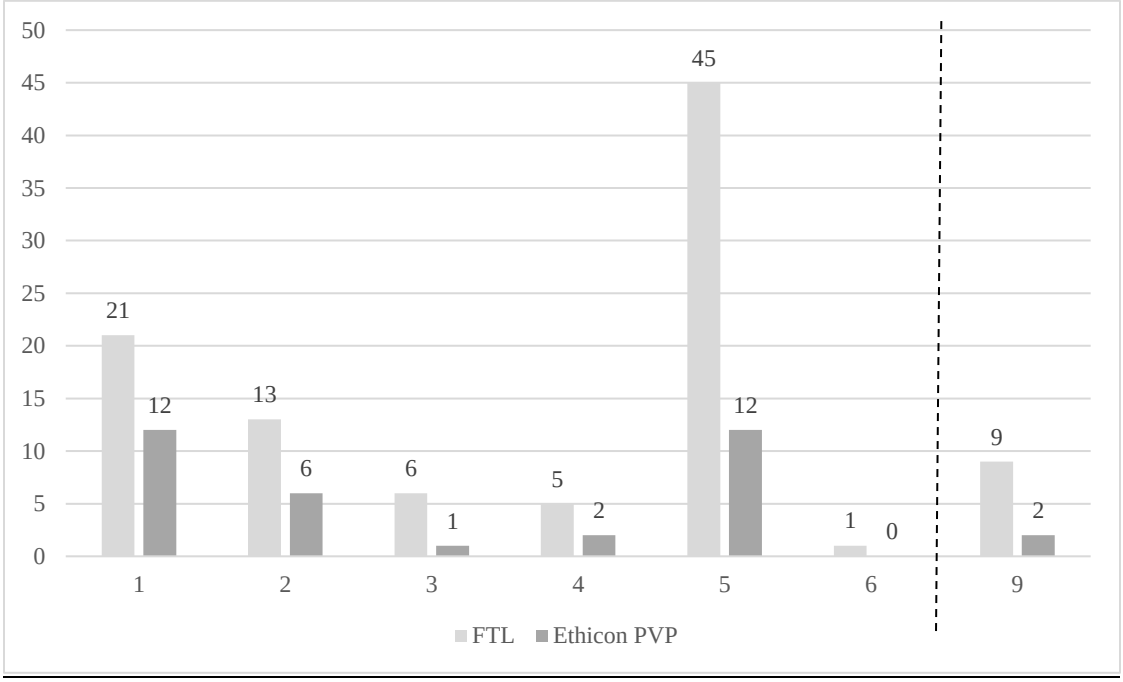


Figure 24: Abbreviated Injury Scale (AIS) Search Screenshot – Hematoma

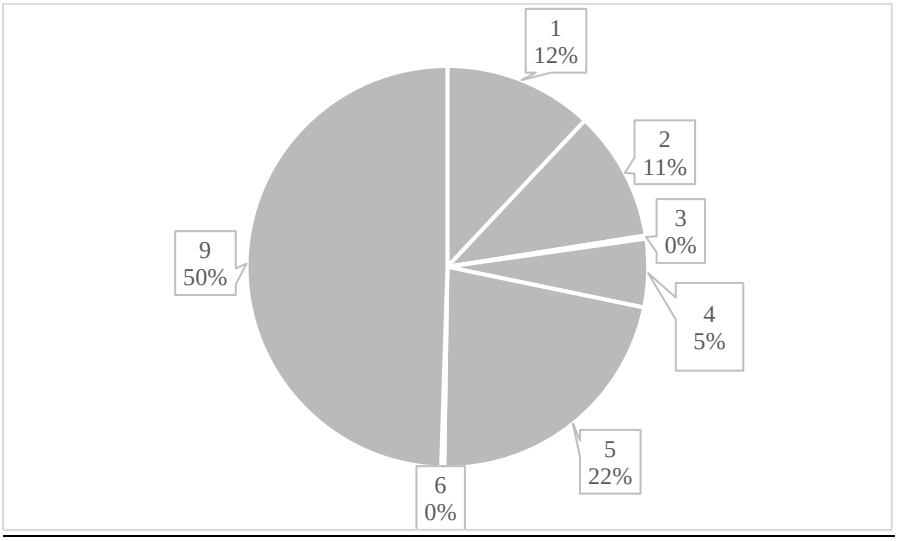
(Association for the Advancement for Automotive Medicine's AIS 2015)



AAAM's Abbreviated Injury Scale (AIS)
(AAAM, 2015)

AIS Code	Description
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximal
9	Unknown

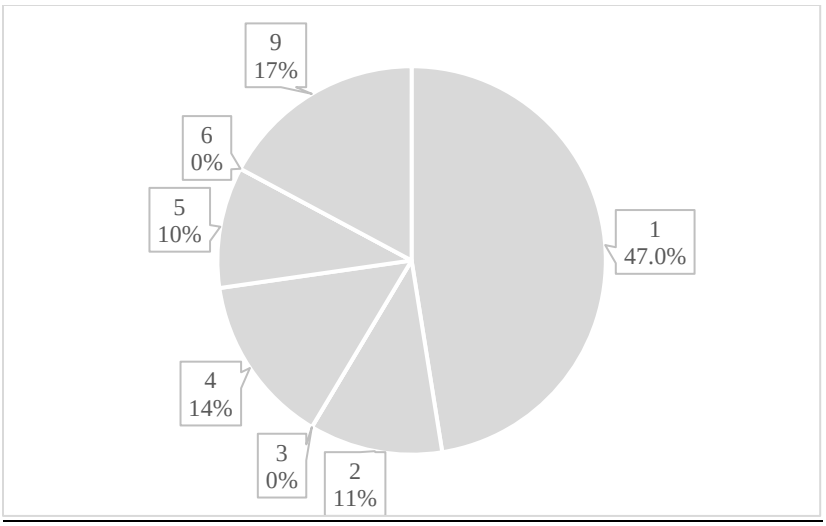
Figure 25:Abbreviated Injury Scale (AIS) Patient Problems FTL Product Category Compared to Ethicon's PVP Medium Mesh



AAAM's Abbreviated Injury Scale (AIS)
(AAAM, 2015)

AIS Code	Description
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximal
9	Unknown

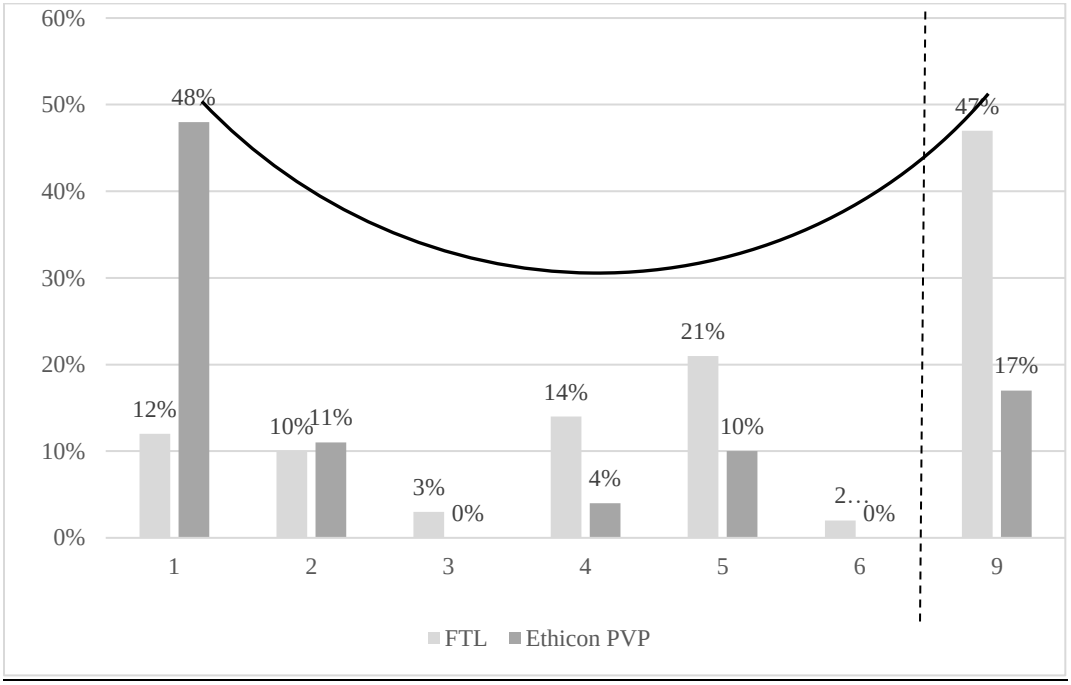
Figure 26: Patient Problems Reported as a Share of the Whole 2021 - 2022 - FTL



AAAM's Abbreviated Injury Scale (AIS)
(AAAM, 2015)

AIS Code	Description
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximal
9	Unknown

Figure 27: Patient Problems Reported as a Share of the Whole 2021 - 2022 – Ethicon PVP Medium Mesh



AAAM's Abbreviated Injury Scale (AIS)
(AAAM, 2015)

AIS Code	Description
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximal
9	Unknown

Figure 28: Abbreviated Injury Scale (AIS) Patient Problems by Proportionate Share - FTL Product Category Compared to Ethicon's PVP Medium Mesh

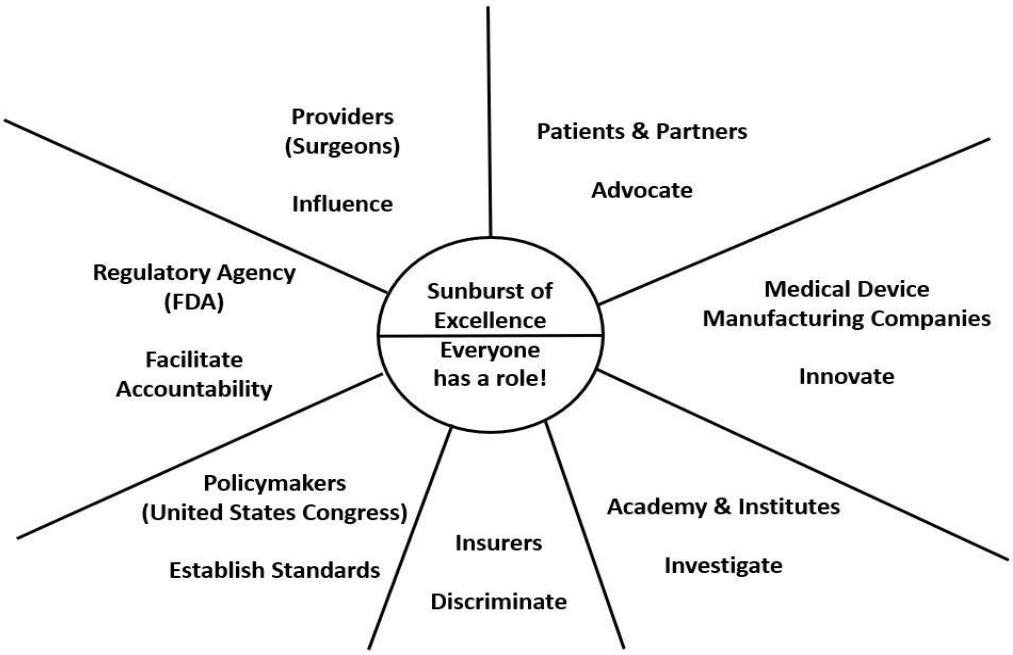


Figure 29: Rectifying the Medical Device Marketplace Sunburst of Excellence

☐ **Have we exhausted all treatment avenues? Is surgery *now* my only option?**

☐ **How many of this device have you implanted into patients?**

☐ **Over what time period have you completed surgeries, like the one recommended to me, with this device?**

☐ **What are some of the minor and major patient problems associated with this device?**

☐ **How many reported deaths have been associated with this implanted device?**

☐ **After implant surgery and I'm healed, what daily physical and qualitative benefits should I expect?**

☐ **To a loved one in my condition, would you recommend this surgery? This device?**

Figure 30: Ask Your Surgeon - Seven to Survive and Thrive Checklist

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