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Regulatory Biomedical Engineering: Application of the Regulatory Science Framework to Biomedical Engineering

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ABSTRACT

Regulatory biomedical engineering is an evolving engineering discipline consisting of the application of regulatory science to biomedical engineering. This paper briefly describes the evolution of biomedical engineering to be followed by the definition of regulatory engineering. In the next section metrics for evaluation of regulatory engineering claims (MEREC) based on best available engineering claims (BARE) are described. The next sections are devoted to the application of BARE/MEREC to biomedical engineering by identifying the three phases of regulatory biomedical engineering and uniqueness of regulatory biomedical engineering. The paper concludes that the application of regulatory biomedical engineering would have improved the process. Several examples are provided indicating the application of three phases of BARS/MERSC.

Keywords: *Best Available Regulatory Engineering, Three phases of regulatory engineering, Jeffersonian Principle, Bjork-Shiley heart valve, Therac-25 CT Scanner, Silicone Breast Implant, Theranos Edison Blood Test Devices, Synthes Norian XR Bone Cement, Olympus Duodenoscopes;*

INTRODUCTION

Although regulatory engineering has been practiced for several decades, only recently it has been recognized as a new engineering discipline. There is a confusion on the nature of regulatory engineering. The most prevalent vision is that it deals with how one complies with regulations notably occupational safety. In fact, regulatory engineering is a part of regulatory science which includes all scientific disciplines ranging from natural sciences, social sciences medicine, to engineering. Regulatory science including regulatory engineering is traceable to certain actions at the Environmental Protection Agency [1} leading to the formation of the Institute for Regulatory Science (RSI) in 1985.

Many engineering disciplines includes activities dealing with regulatory engineering. Consequently, there are regulatory mechanical; engineering, regulatory chemical engineering, regulatory civil engineering etc. Probably the engineering profession that recognized regulatory engineering was American Society of Mechanical Engineers, also known as ASME International. There is a widespread confusion on the definition of regulatory science including regulatory engineering. The Food and Drug Administration [2] defines regulatory science as

Regulatory science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality and performance of all FDA-regulated products.

There are several similar definitions by the National Academies [3] consisting of the National Academy of Sciences, National Academy of Engineering and the National Academy of Medicine. The conversion of the FDA definition to regulatory engineering would result in the following definition

Regulatory engineering is a discipline consisting of the development and application of engineering methods, tools, approaches, and other relevant processes derived from various engineering disciplines used to support regulatory and other policy objectives.

The classical evolution of technology based on engineering research follows a four- steps process. As shown In Figure 1, the process starts with research, typically leading to a publication. As many published scientific and engineering

claims prove to be not reproducible, the next step attempts to validate the claim. The third step consisting of pilot plan attempts to scale up the process. There is a major difference between many parameters in laboratory scale and production- scale activities. For example, heat transfer in the laboratory -scale studies are reasonably fast. In contrast, heat transfer in production from one point to the entire production is of concern. In the past and to some extent today, pilot plant consisted a reasonably large-scale facility. Meanwhile the advancement of mathematical modeling has significantly reduced the need for a physical pilot plant. However, regulatory engineer needs to know the level of maturity and the level of reliability of engineering. The following process addresses these needs.

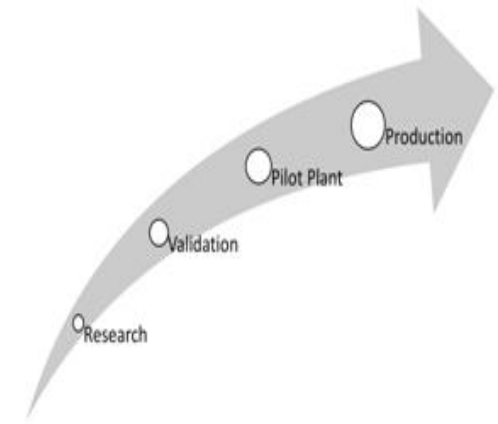

Figure 1. Evolution of Technology

Based on the definition of regulatory science, regulatory engineering can be defined as follows:

Regulatory engineering consists of applied version of various engineering disciplines

The community of regulatory engineering including Regulatory bioengineering consists of the following

- Regulatory Agencies at federal, state, and local levels use regulatory engineering including biomedical engineering to promulgate regulations, apply them to Licensing/permitting, and enforce them
- Regulated Community covering those industries apply regulatory engineering including biomedical engineering in their operation
- Engineers individually as well as their professional organizations. This group is the key contributor to regulatory engineering including regulatory biomedical engineering

Regulatory biomedical engineering covers a broad spectrum of engineering. For example, there are mandated control technologies, protective gears used in operations that may expose individuals to microbiological agents, x-ray equipment used in medicine, equipment used in knee replacement surgery, or engineering processes used in biomedical operations.

This paper starts by addressing fundamentals aspects of regulatory engineering. In the next step the uniqueness of biomedical engineering is briefly addressed. Subsequently several examples of poorly managed of biomedical engineering are provided. The paper concludes by identifying shortcoming of lack of attention to the uniqueness of biomedical engineering.

Metrics for Evaluation of Regulatory Engineering Claims

Metrics for Evaluation of Regulatory Engineering Claims (MEREC) were developed based on Best Available Regulatory Science and Metrics for Evaluation of Regulatory Scientific Claims [4] to address the unique nature of regulatory engineering and provide avenues for addressing its needs. As shown in Figure 2, MEREC is based on five general principles of Best Available Regulatory Engineering and three pillars as follows:

Open-Mindedness Principle

Every claim on a discovery; development of a new technology; or identification of a potential human health problem; requires the willingness to carefully evaluate the claim. Although this principle is a key to all technological advancements the past theocracies, governmental agencies, and many others have rejected an idea because of the lack of appreciation for innovative processes.

Skepticism Principle

It is incumbent upon those who make a technical claim to provide sufficient evidence supporting their claim. There is no contradiction between this principle and the *Open-Mindedness Principle* as the technical community has developed well-established processes to provide opportunity to those who make a claim to provide the necessary evidence.

Note that the USEP play a key role in reaching the balance.

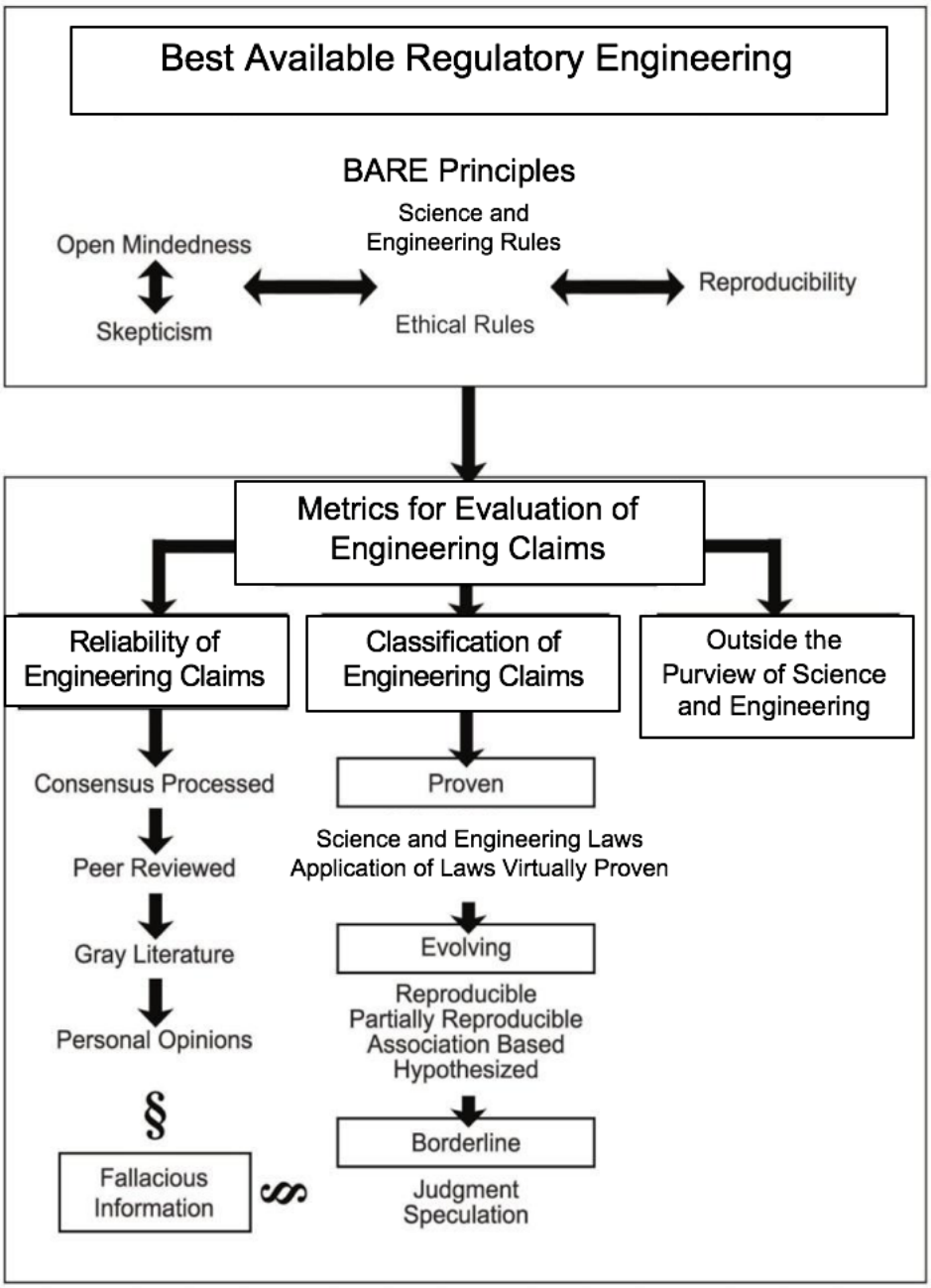

Figure2. *Structure of Metrics for Evaluation of Regulator Engineering*

Engineering Rules Principle

One of the most important subjects in MEREC is compliance with Engineering Rules Principle. All scientific and engineering disciplines use certain methods, processes, and techniques in pursuit of their technical activities.

Ethical Rules Principle

This principle covers several elements including truthfulness, communicability, and transparency and engineering ethics. This Principle requires that those who make an engineering claim must describe their assumptions, judgments, or default data in a language that is understandable to the affected communities. In addition, they must also describe if their engineering claim includes areas outside the purview of science and engineering.

Violation of this principle is one the primary reasons for disagreements of technical foundation of policy decisions and numerous other areas of public interest.

Reproducibility Principle

The ultimate proof of the validity of a claim dealing with technical information is to be

reproducible by those who have the necessary competency and the needed equipment and facilities.

Pillar I. Classification of Engineering Claims

One of the primary reasons for the uniqueness of regulatory engineering is the need to consider the level of maturity of a regulatory engineering claim. Surely one would have more confidence in a claim that is based on a scientific law as compared to a judgment of an engineer or a scientist.

Proven Science and Engineering

The cornerstone of this class is compliance with Reproducibility Principle implying that any investigator who has the necessary skills and the proper equipment can reproduce it. Therefore, this class of technical information does not require assumptions or any other conditions for its validity. This class includes also those segments of applied sciences and engineering that are entirely based on scientific laws and exclude assumptions.

Evolving Engineering Claims

The overwhelming technical advances in virtually all disciplines are evolving engineering claims. As the following description shows one can identify many groups within this class, however, it is likely most of these would be a subpart of the following classes.

Reproducible Engineering Claims

Reliable information dealing with a subject that is not completely understood constitutes the core of this class. The engineering claim in this class must comply with Reproducibility Principle. Advancements in various engineering; and related disciplines are based on the desire of investigators to improve knowledge in this class.

Partially Reproducible Engineering Claims

This class consists of an extension of the applicability of a technology or an engineering activity beyond its original design.

Association Based Engineering Claims

This class is based on the notion that comparing two engineering techniques one functioning and other one not functioning can lead to the assessment of the cause of failure.

Hypothesized Engineering Claims

As the title implies this class attempts to convert an observation or thought to a potential technology or an engineering activity.

Borderline Engineering Claims

In many cases the society is facing a decision to take or not take an action without having any engineering information. The two classes in this category are

Technical Judgment

If a decision must be made without having the needed information, the necessary data, or other technical requirements a process known as expert judgment is used. It consists of asking several presumably knowledgeable individuals to give answers to specific questions and statistically assess the results. Note that information in this class is often an educated guess.

Speculation

This class consists of information that cannot meet standards described in any of the above classes. It is often based on the intuition of an individual who wants to stimulate a discussion or initiate a research project.

Fallacious Information

This class is the engineering version of "pseudoscience", "junk science", or "politically-processed science". There are those who justify the dissemination of Fallacious information on basis that it is necessary to exaggerate a problem in order to move the population to accomplish a noble goal. What is being overlooked is the long-term damage that misinformation causes.

Pillar II: Assessment of the Reliability of Engineering Claim

One of the key issues in managing regulatory engineering is the reliability of technical information. A regulator, a judge, a legislator, or those who are being regulated must be convinced that the technical foundation of the regulatory decision is sound. The reliability of regulatory engineering, can be categorized as follows:

Personal Opinions

Expression of views by individuals regardless of their training, experience, and social agenda, or their technical validity is the foundation of a free society.

Gray Literature

Written information prepared by government agencies, advocacy groups, and individuals that have not been peer reviewed falls in this

category and often is the written version of personal opinions.

Peer Reviewed Engineering Claim

The value of peer review and similar processes in assessing the validity of technical assertions has been known for at least two centuries. Peer review is used routinely by editors of technical journals to accept, reject, or ask for revision of a submitted manuscript. It is also the standard process used by funding agencies to evaluate a submitted request for funding. Independent peer review is also truly the only option to evaluate regulatory engineering claims.

Consensus-Processed Engineering Claim

This category consists of information resulting from a process used to resolve disputes, particularly those in contested areas of regulatory engineering. This process is particularly useful for information that includes assumptions, judgments, inclusion of default data and other areas.

Pillar III. Areas outside the Purview of Science and Engineering

One of the most complex and often misused or abused area of regulatory engineering is the intrusion of societal goals, ideology, and numerous nontechnical subjects in regulatory engineering decisions. The intrusion of religion, ideology, or any other societal objective in the regulatory engineering process inherently jeopardizes the objectivity and consequently the acceptability of technical information. The role of the engineer is to provide engineering options that underlies a potential regulatory decision. Although the religious, cultural, and tradition of various countries such as US, India, China, Germany, Brazil, Israel, or Saudi Arabia are different, the engineering foundation of a regulatory decision, with few exceptions, should be identical in these countries.

Application of Regulatory Biomedical Engineering

A detailed description of application of regulatory engineering disciplines is far beyond the scope of this paper. However, it should be recognized that there are numerous areas that are common to all regulatory engineering disciplines. Instead, this paper emphasizes regulatory biomedical engineering. Many regulatory biomedical engineering models and technologies resulting from them fall in Partially Reproducible and lower classes. Therefore, it is imperative to ensure that

- Uncertainties, judgments the inclusion of default data and similar areas in the decision process are clearly and unambiguously identified.
- The biomedical regulatory engineering decisions should exclude areas outside the purview of science and engineering and if not excluded, their inclusion must not only be justified but their details are identified and described.
- Precisely because of the nature of regulatory biomedical engineering it is imperative that all regulatory biomedical engineering documents are subjected to independent peer review.
- Many decisions that include regulatory bioengineering are based on the desire of the regulators to protect the affected community and the public. One of the primary tools to assess potential harm is risk assessment.

Jeffersonian Communication Principle

William Ruckelshaus the first administrator of the Environmental Protection Agency (EPA) who returned to the EPA during the Reagan administration to address resolve major Problems introduced the concept of Jeffersonian Communication Principle by quoting Thomas Jefferson, the third president of the US [5].Jeffersonian Communication Principle categorizes the recipient of technical information into the following

The first group consists of specialists in biomedical engineering particularly regulatory biomedical engineering. Another group is the general public, sometimes refereed to as six graders. The Jeffersonian Principle provides a process to implement the Ethical Rues Principle of Regulatory Engineering by requiring that regulatory biomedical engineering information must be translated in a language that is understandable to knowledgeable non-specialists. Engineers, scientists, elected individuals, and appointed officials overwhelming fall in this category.

Three Phases of Regulatory Biomedical Engineering

Much like regulatory science [1] the application of regulatory bioengineering is based on three phases follows:

During the first *Initial Phase* regulations are promulgated although the needed scientific and bioengineering information is less than adequate. The decisions in the phase are based on following:

- There are legal mandates with a deadline.
- A device or equipment is needed to save human life and there is no alternative for that item.
- The approval would enhance the quality of life

During the second *Exploratory phase* an attempt is made to enhance the relevant knowledge. In addition, the bioengineering consequences of the first phase are evaluated. In many cases, research and development are initiated with the objective not only to evaluate the initial decision but to evaluate potential alternatives.

Finally, during the *Standard Operating Phase*, the results of the second phase are used to reach a decision that improves the reproducibility of the objective of the approved item. There is ample evidence that in many cases that *Standard Operating Phase* decisions may have to be reevaluated based on evolution of technology, replacement of a segment of a device or other reasons. However, in effect the process consists of repeating the second phase.

If probably performed, the application of the three phases would move the level of maturity of MEREC. In order words the process would improve the reproducibility of applied biomedical engineering.

Examples of Experience with Regulatory Biomedical Engineering

There are many instances in which regulatory biomedical engineering played a direct role in the success or failure of a biomedical technology. A description of the contribution of engineering profession to the evolution and application of many successful devices, equipment and other useful items is too large to be included in this paper. Instead in the following certain examples are identified that describe distinct situations of the regulatory process applied to medical instruments, prosthesis, radiation technologies, and physical implants.

Bjork-Shiley heart valve

This heart valve was a prosthetic designed to replace the aortic or mitral valves [6]. The design involved a single carbon-coated disc which was held in place by two metal struts. These struts, inflow and outflow, responded to pressure changes in blood flow. The problem occurred when multiple manufacturing failures, due to fractures in the outflow strut because of welding, were seen during premarket trials. The FDA approved the prosthetic device after Shiley ensured that the failures were just random occurrences.

During the second phase of regulatory bioengineering it was shown that the fracture of prosthetic device was caused by an imbalance of forces between the disc closing and opening. Consequently, the patients suffered from cardiac death due to unregulated blood flow. Furthermore, during this phase he manufacturing problem identified in the first phase was significantly more severe than random occurrence. Consequently, the application of the device during the seven years its implantation resulted a total of 500 cases reported, two-thirds of which ended in death [7].The device was recalled in November 1st, 1986, seven years after the first patients had received the implant.

It is likely that the application of regulatory bioengineering process would have prevented or at least minimized the number of deaths associated with prosthetic heart valve. The manufacturing problem should have been investigated further and addressed earlier during Initial or Exploratory Phases of regulatory bioengineering.

Therac-25 CT Scanner

In a period of two years, June 1985 through January 1987, the Therac-25 radiation therapy machine caused patient-involved accidents by administering radiation above the necessary dosage [8]. This overly high admission of radiotherapy was the cause of six unfortunate outcomes. In 1985, a 61- years old woman receiving breast cancer treatment immediately felt burning sensation in area of treatment. She was sent to the hospital and later lost both breasts as well as feeling in her shoulder due to overexposure caused by the malfunction in the CT Scanner. In the same year, a 40-year old patient received her 24th Therac-25 treatment at Ontario Cancer Foundation clinic. After the scanner had incorrectly displayed that no dose had been administered, the operator followed by pushing the dose button multiple times. This led to over-exposure to radiation in the patient's hip and subsequent death.

Another case occurred at the Yakima Valley Memorial Hospital where the patient experienced red stripes in treatment area but continued to receive exposure. Eventually, the patient required surgical treatment to amend the damage caused by over-exposure to radiation. The following year, (1986), an additional accident occurred at East Texas Cancer Center. In this instance, the operator typed in X-ray mode treatment instead of electron-mode. In another case, the machine provided a message stating an under-dose. The operator responded by continuing to provide exposures, not knowing that the patient was suffering from over-exposure. Consequently, the patient lost the use of his left arm and both legs, was unable to speak, and had several other complications until he eventually died. The East Texas Cancer Center was the setting of another case. In this situation, the operator entered the wrong mode of treatment. The patient endured a coma and suffered from neurological problems which preceded his inevitable death. In 1987, the last case took place at the Yakima Valley Memorial Hospital. Again, in this case, the machine malfunctioned leading to the patient's death.

These cases describe events that occurred in the Initial Phase of Regulatory Engineering. The evaluation of these events during the Exploratory Phase led to reprograming ofthe Therac-25 CT Scanner with the objective to eliminate the potential for overexposure to radiation. The only truly shortcoming of the regulatory biomedical engineering process was the length of Exploratory Phase.

Silicone Breast Implant

The example of the silicone breast implant is another circumstance in which the FDA was aware of adverse effects caused by the implant, but still approved the device, first in 2006, for market entry [9]. Post-approval studies by manufacturers were required by the FDA to gather information on any adverse health effects. Some of the problems endured by patients involved in the post-approval studies involved internal rupture, cosmetic issues such as wrinkling or scarring, pain, and infection. Most of these events led to reoperation or implant removal. As identified by the FDA [9]post-surgery evaluations demonstrated that approximately one out of every five first-time patients required implant removal.

During the Exploratory Phase post-market analysis was performed. Subsequently the FDA stated, "Based on the totality of the evidence, the FDA believes that silicone gel-filled breast implants have a reasonable assurance of safety and effectiveness when used as labeled. Despite frequent local complications and adverse outcomes, the benefits and risks of breast implants are sufficiently well understood for women to make informed decisions about their use". Obviously, the FDA recognized potential adverse effects, but decided that patients should make decision on acceptability of potential risk.

Theranos Edison Blood Test Devices

The case of Theranos and their portable blood test analyzers, referred to as Edison constituted a reevaluation of Standard Operating Phase of regulatory engineering. Theranos claimed that Edison could use a single drop of blood and accurately analyze up to 70 different markers with results sent to a mobile device within a matter of hours, and all at less than half the cost of the Medicare reimbursement rate. The device used a proprietary "nanotainer" to collect a blood sample. However, in April 2015, they could not produce evidence to show that lab staff had tested the instruments before using them on customer samples. Theranos ended up having to cease its usage after criticism that it had not been approved or evaluated by the FDA [10].

In January of 2016, the Centers for Medicare and Medicaid Services (CMS) reported that one of their labs "did not comply with certificate requirements and performance standards" which caused "immediate jeopardy to patient health and safety" [11]. Theranos, aware of this, diluted samples and ran them through traditional blood testing machines manufactured by Siemens - the predominant blood testing machine on the market. This led to a criminal investigation by the SEC for misleading investors and government officials about its technology [12]. A federal inspection report claimed that a Theranos lab had run 81 blood tests on patients despite disparities in the results from quality control checks [13]. They did this over a period of six months and inaccurate test results were negatively affecting medical decisions. Theranos had a prevailing tendency for severely unsafe and unsatisfactory lab practices, even after being told to correct them by agencies such as CMS

Eventually the misdeeds of Theranos reached the public media, The *Wall Street Journal* reported that the e Edison devices could not

accurately detect enough molecules in blood samples to provide an accurate reading [14]. Further accusations that Theranos was faking results come from a former investor who filed a lawsuit claiming they had used a shell company to discreetly purchase laboratory equipment to run fake demonstrations [15].

The transgressions of Theranos do not end there, in April 2015, they could not produce evidence to show that lab staff had tested the instruments before using them on customer samples. In January of 2016, the Centers for Medicare and Medicaid Services reported that one of their labs "did not comply with certificate requirements and performance standards" which caused "immediate jeopardy to patient health and safety" [11]. Their findings were so severe that the lab could lose access to Medicare patients. Eventually, the leadership of Theranoshad to deal with major court cases and other adverse events.

There are two key problems associated with this case. During the Initial Phase the biomedical engineering claims could have been better evaluated. However, the regulatory agencies face the problem of comparing potential benefits of a technology with its potential shortcomings particularly if an applicant is not truthful. The regulatory agency is not expected to reproduce every experiment claimed by an applicant. However, the Exploratory Phase should have been shorter.

Synthes Norian XR Bone Cement

Synthes, a medical device company and a subsidiary of Johnsonis the manufacturer of Norian XR bone cement which upon injection is converted to bones in the human skeleton. Although the [16] explicitly instructed Synthes not to advertise Norian XR for certain some spine surgeries they proceeded to do so resulting in five known cases of death. Subsequent interviews with former employees and surgeons, court transcripts, and company documents showed Synthes disregarded numerous warnings about their practices and a disregard of concerns of on-staff scientists who were worried that the cement could cause fatal blood clots [17].Obviously, the company violated the rules governing the regulatory process. They used a process that was specifically not approved and neglected to inform the patients on potential risks. Not surprisingly, the leadership of the company faced judicial problems. This case demonstrates failure during the Initial Phases of the process

Contamination of Olympus Duodenoscopes

Duodenoscopes are flexible tubes that can inserted into mouth and moved to throat and stomach into the top of small intestine. The manufacturer has been criticized for having a design flaw that makes them difficult to sterilize the device. This design flaw has reportedly lead to the deaths of 35 patients who developed infections following procedures using the device. Several lawsuits against the company related to an infectious disease outbreak in a Seattle hospital [18]. The company is accused of design flaws in their scope had their premarket validation testing. Another misstep by the company was not informing hospitals experiencing outbreaks of previous outbreaks that had been reported to them in various other locations. Seemingly to downplay or hide the fact that this was a recurring problem with their device

The events associated with this device occurred primarily in Exploratory Phase. Again here, the speed of recognition of problems would have reduced adverse consequences of application of this device.

Cybersecurity of St. Jude Pacemakers

St. Jude's implantable cardiac pacemakers function with the assistance of a configurable computer system that was found to be vulnerable to cyber intrusions such as hacking. While there have been no complications associated with the pacemaker, the vulnerability is significant as it has the potential to affect about 465,000 individuals with an implant. The FDA conducted a review to screen the potential gaps in the cybersecurity of the pacemaker and found that such gaps could be exploited to give access to an unauthorized user using only commercially available equipment. St. Jude responded by developing a firmware update to address the security concerns of its pacemaker. Eventually the FDA [19] approved this firmware update for roll out.

As medical devices, hospital networks, and medical records databases become more interconnected through information technology and the internet, important cybersecurity issues will arise and need to be addressed. It is essential that manufacturers in the biotechnology industry understand and implement strong cybersecurity protocols. St. Jude pacemakers are in Standard

Operating Phase. However, the occurrence of cyber intrusion requires a modification of the device which normally occurs in Exploratory Phase identifying the need to consider the level of maturity of regulatory engineering as described in BARE/MEREC.

A potential scenario elucidates the importance of cybersecurity. A medical device such as a pacemaker that has been implanted in hundreds of thousands of individuals is hackable to the extent by which every device in the country could quickly be turned off. The resulting catastrophe would mirror that of a weapon of mass destruction.

Therefore, it is paramount that biotechnology communities consider cybersecurity seriously.

Conclusions

The biomedical engineering, as currently administered has saved many lives, reduced pains, and enhanced the quality of life for a large segment of the public. However, as the above examples demonstrate there is a need to recognize the level of maturity of engineering and inherent uncertainties in predicting certain engineering processes. Biomedical engineers must recognize that engineering used in biomedical system falls in one of the classes of Evolving regulatory engineering Claims. Consequently, the three phases of regulatory biomedical engineering provide an opportunity to improve the reproducibility of engineering claims. Furthermore, the technical information used in the decision process must be translated to a language that knowledgeable non-specialist, and hopefully the affected community can understand. It is likely that such an approach will increase the participation of knowledgeable non-specialist in the decision process and reduce potential problems

Conflict of Interest

The authors express no conflict of interest

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