Cybernetics Approach to Enhancing Technical Entrepreneurship and Engineering Management Programs for Biotechnology Innovation

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***Abstract*— In the biomedical industry, unmet clinical needs necessitate research and technology innovation for human application, but innovation, and subsequent technology based entrepreneurial endeavors, lend themselves to a unique variety of challenges, even more so when the technology is intended for human application. Technologies intended for human use are highly regulated, as are the companies that design, develop, manufacture, and distribute these biomedical technologies; the intent of the regulations being to ultimately ensure patient safety. Engineering management and Technology Entrepreneurship programs have largely provided the management know-how and the science and engineering skills to address the uniqueness of a technology venture. However, these programs have not, on the whole, integrated the necessary interdisciplinary content into their curricula to address the explosion of new or changing regulations, and their impact on the stages of the entrepreneurial lifecycle. It requires a unique skillset and knowledge base to navigate the regulations and understand the level of influence on each phase of the entrepreneurial venture. This paper describes a cybernetics approach to enhancing Technical Entrepreneurship courses or Engineering Management programs, caused by the need to properly prepare and equip regulated biotechnology innovators and entrepreneurs to navigate the complexities of the regulatory environment, de-risk the regulatory threats to the enterprise, and accelerate the commercial viability of innovative biotechnology, for human use.**

***Index Terms*— Engineering, Education, Medical Device, Biotechnology, Entrepreneurship**

I. BIOTECHNOLOGY INNOVATION AND ENTREPRENEURSHIP - INTRODUCTION

According to the Global Entrepreneurship Institute's Global Community for Advancing Studies in Entrepreneurship, The Entrepreneurial Life Cycle is applicable to all business types, from small, informal start-ups to large, corporations. The cycle starts with an idea or 'perceived opportunity, creates an organization to pursue it, assembles the required resources, implements a practical plan, assumes the risks and the rewards, all in a timely manner for all involved'[1]. The stages of the entrepreneurial cycle are described by the Entrepreneurship Institute and pictorially represented in figure 1.

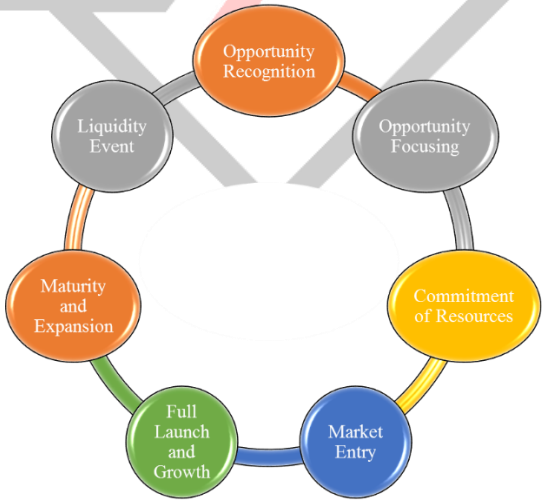

Figure 1 Entrepreneurial Life Cycle

According to some experts, experienced with successful technology based entrepreneurial endeavors, there is a real limitation in university entrepreneurship programs to provide true experiential learning for technology ventures; stating that technology management, and technology entrepreneurship are unique and not addressed by typical business management courses. Combining engineering and management knowledge into Technical Entrepreneurship programs that integrate the unique real-world problems arising in technical businesses, as opposed to focusing on purely business topics, has proven highly successful; enabling the

technology based entrepreneur to thoroughly understand the underlying technical issues, processes, and procedures while also learning the non-technical areas of entrepreneurship.

In the biomedical industry, unmet clinical needs necessitate research and technology innovation for human application, but innovation, and subsequent technology based entrepreneurial endeavors, lend themselves to a unique variety of challenges, even more so when the technology is intended for human application. Technologies intended for human use are highly regulated, as are the companies that design, develop, manufacture, and distribute these biomedical technologies; the intent of the regulations being to ultimately ensure patient safety. So, regulations define how these products get into clinical use and stay in use; with required regulated outputs spanning the entire lifecycle. These regulated outputs are what moves the development process from one phase to the next, and the variable specificity of these outputs depends on the type of company, geography of venture, intended geographies to market the product, sophistication of the device, its intended use, the associated risk to the end user and the current regulatory environment, to name a few.

The increased need to further innovate biotechnology and deliver this technology through entrepreneurial endeavors is driven by people living longer and the associated new healthcare demands. However in the regulated industry, new technologies are outpacing regulations laws, and regulatory guidance, causing an expansion in the volume and complexity of the regulations and subsequently, an increase in the number of regulatory bodies providing oversight of biomedical technologies companies. To complicate things further, these regulated considerations may or may not be leveraged to satisfy global regulatory requirements. Every global geography is different and constantly changing as new technologies outpace the regulations, or new post-market information is gained about the performance of current or similar technologies in different geographies.

The combination of new biotechnologies, global regulatory expansion, and regulatory requirements, in a seemingly continuous state of flux, have dramatically changed the regulatory landscape; creating new complexities for companies, affecting the innovation - to - commercialization pathways and timelines. According to the FDA, the US government agency that regulates these biomedical technology companies, 'better understanding of regulatory processes will accelerate the delivery of innovative medical devices to patients'[2].

There is no such thing as a one-size-fits-all approach to understanding and implementing the practice of regulations, just as there is not a one-size-fits-all approach to any entrepreneurial venture. As is true for a technology venture, it requires a unique skillset and knowledge base to navigate the changing global regulated minefield of "it depends" pathways, and understand the level of influence global regulations, and associated expectations, play on a biotechnology entrepreneurial venture and the design, development, manufacture and distribution of a biotechnology innovation.

Engineering management and technology entrepreneurship programs have largely provided the management know-how and the science and engineering skills to address the uniqueness of a technology venture. However, these programs have not, on the whole, integrated the necessary interdisciplinary content into their curricula to address the explosion of new or changing regulations, and their impact on the stages of the entrepreneurial lifecycle.

This lacking education lends itself to the failure of these programs to equip and prepare biotechnology innovators and entrepreneurs to navigate the increased complexity of this modern regulatory landscape, address the nuances of the biomedical industry, and lead the delivery and preservation of innovative technologies and entrepreneurial endeavors that can withstand intense regulatory scrutiny while satisfying the clinical needs and stakeholder expectations.

II. Biotechnology Innovation and Entrepreneurship – The Concept Methodology

Often overlooked, stages in the Entrepreneurial Life Cycle are heavily influenced by regulations for products such as medical devices, pharmaceuticals, food, cosmetics, and the like, as shown in figure 2.

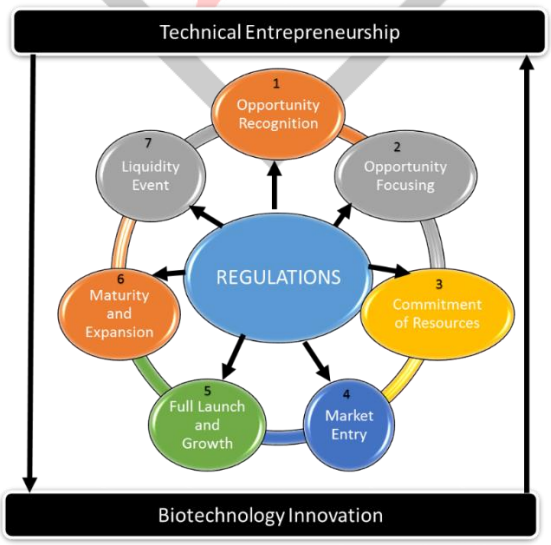

Figure 2 Regulatory influence on stages of entrepreneurial life cycle

It requires a unique skillset and knowledge base to navigate the regulations and understand the level of influence on each phase of the entrepreneurial venture. For example, a biomedical device venture will face certain regulatory considerations that will inform actions and outputs of the stages of the Entrepreneurship lifecycle, a few examples are described below:

In stage one, regulations are a dimension of the opportunity recognition in that they inform the design concept about the associated regulatory pathways to market, including influence on all other phases of the lifecycle. For example, In the US, products will be placed into a regulatory classification. The sophistication of the device, and what a company wants to claim about the device, determines the "risk" of the device, and subsequently, the device classification. This classification carries with it variable levels of regulatory controls for the device design, development, manufacture, and distribution, as well as controls on the company, as a whole. Since the classification of a technology for an intended use is based on a predicate system (comparison of like or similar technologies), it's important to incorporate regulatory analysis into the research when determining if the opportunity is attractive, or not.

In stage two, as part of the "sanity check" during opportunity focusing, the regulatory, reimbursement and clinical strategies should be considered in the go/no-go determination. These strategies will reveal relevant gaps in the business plan and provide information about likely constraints that can impact the focus of the company.

Certain resources and associated levels of regulatory controls are required for a regulated product, above and beyond those of a non-regulated products, as well as for the company intending to market that product. During stage three, it's important to understand what those controls are, how they affect resources and business operations in a way that could make or break the ability of the product to reach a global market, and what continued controls are necessary to keep that product on the market. For example, design controls, as detailed in the US Code of Federal Regulations, and activities, such as certain verification testing expected by the regulatory agency, are in fact necessary and must be robust, and in turn, can be expensive and time consuming. As well, the intended market geographies may have certain design control expectations, such as in-country testing. Knowledge of the global regulatory environment and regulatory expectations can help to adequately plan resources.

Entering the market for a regulated product means first having approval from regulatory authorities to do so. Those approvals are dependent on the controls used in the methods, facilities, and resources used to design, develop, manufacture and distribute the product. Depending on the type of product and the intended claims about that product, these requirements are different and frequently changing. Without proper regulatory considerations during stage four, market entry, and therefore profitability, are threatened.

There are certain regulatory advantages to being a small company vs. a large company, such as reduced regulatory user fees, and should be considered during stage five. These differences can be significant. For example, as described by FDA Fiscal Year 2018 Medical Device User Fee Amendment's User Fees, the user fee for a small business attempting to market a moderate or high risk device is 75% less expensive than that of a larger company; an initial premarket approval application cost is $310,764 and for a small business is $77,691 [3]. To qualify for reduced fees, there are certain criteria that must be met, e.g. total gross receipts. Different criteria are applicable to foreign business and it's not enough to simply meet criteria. There are specific actions required to demonstrate how criteria are met, and regulatory applications to formally request 'small business' status. This should be considered when entrepreneurs are determining their high-growth strategy. Another example of how regulatory requirements might influence the high growth strategy relates to growth of the scope of the establishment, or enhancement of production and management systems. Plans to grow the manufacturing capability, for example, could threaten your product approval for a higher risk device, or could also threaten your international approval if not handled properly, such as with certain required testing and a regulatory supplements to the original application. Expanding your establishment scope could confine your establishment into a different establishment type, as defined by FDA, which have different implications on your business operations.

Without doubt, there are significant regulatory considerations when considering global expansion, acquisitions, and mergers, stage 6. For example, it can cause significant problems to acquire a company with an ineffective or inadequate quality management system that can lead to an FDA warning letter, product recalls, consent decrees, and/or civil and money penalties. Some of the most concerning problems can include: diversion or increase in resources, delay to new product introduction, damage to a company's reputation, competitor leverage, and possibly even loss of business. Likewise, merging with a company that unknowingly has an adulterated product, e.g. does not have appropriate regulatory approval, or transferring a product approval that has an incomplete design history or design controls, can cause unforeseen problems. This can result in years of unplanned resource drain to defend unanticipated post market performance, make required design changes and subsequent submissions, and possibly face product removal from the market, altogether.

Finally, in stage seven, depending on what occurred during the maturity and expansion stage, exiting the business can be influenced by regulations in a variety of ways. Having to exit because of regulatory issues, such as those mentioned in stage six, can, of course, lower an initial public offering, or reduce a negotiation position when implementing the exit strategy. Additionally, if exiting by becoming acquired, adequately meeting certain regulatory controls can increase a negotiation position.

III. Interdisciplinary Biotechnology Innovation and Entrepreneurship Program - The Academic Methodology

As the regulatory landscape changes, so do the demands on regulatory professionals, biotechnology innovators and entrepreneurs.

Universities have largely provided the science, engineering and management curricula in Technical Entrepreneurship and Engineering Management programs that drive the technical capabilities and aspirations to deliver variable biotechnology innovations. However, these curricula have not, on the whole, integrated the necessary interdisciplinary content into their programs to address the explosion of new or changing regulations, and their impact and application throughout all critical stages of the lifecycle and, holistically, throughout the biotechnology business. This lacking education lends itself to the inability of universities to consistently and reliably bridge the gap between what is being taught in an academic environment, and what is needed to prepare and equip the next generation of innovators to effectively bring a product to market. This deficiency is a global problem that seriously affects our ability to deliver and sustain critically needed biotechnology solutions in a timely manner.

Engineers, regulatory professionals, management professionals, innovators and entrepreneurs must be equipped to navigate the increased complexity of the modern regulatory landscape, address the nuances of the biomedical industry, and lead the delivery and preservation of innovative technologies that can withstand intense regulatory scrutiny while satisfying the clinical needs and stakeholder expectations. Adding on to the previous research of the author, augmenting Technical Entrepreneurship or Engineering Management programs with the domain specific practice of regulation throughout critical stages of the Entrepreneurial lifecycle is key to addressing this unmet need.

Figure 3 demonstrates a cybernetics approach to enhancing Technical Entrepreneurship courses or Engineering Management programs, caused by the need to properly prepare and equip regulated biotechnology innovators and entrepreneurs to navigate the complexities of the regulatory environment, de-risk the regulatory threats to the enterprise, and accelerate the commercial viability of innovative biotechnology, for human use. The implicit circle within Technology Entrepreneurship and Biotechnology Innovation is the Entrepreneurial lifecycle. The loop on the right represents a series of course options, with outputs of one becoming inputs to the next. The combined result is potentially part of the cybernetic relationship between the Entrepreneurial lifecycle, and courses that teach and practice the regulatory skills necessary to move from one stage to the next, in the biotechnology enterprise.

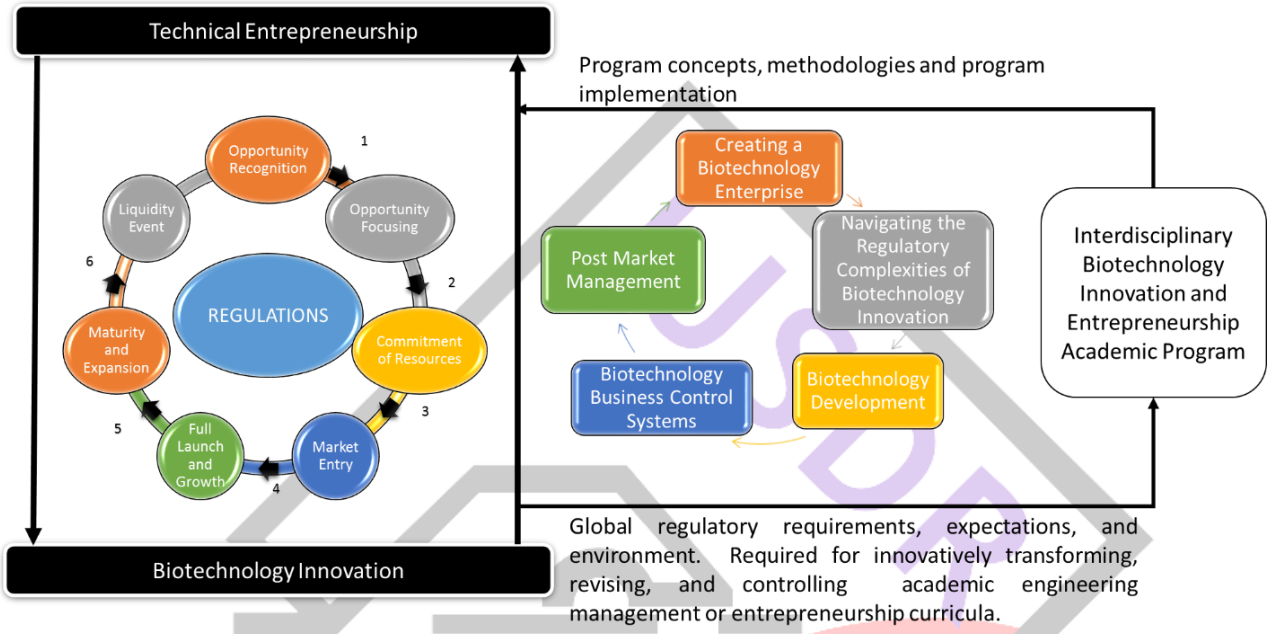

Figure 3 Cybernetic relationship between the Entrepreneurial Lifecycle and Regulatory centric courses to produce an Interdisciplinary Biotechnology Innovation and Entrepreneurship Academic Program

Knowledge and experience with the global regulatory requirements, expectations and environments are required to innovatively transform, revise, or control and academic biotechnology innovation course or engineering management program. Program concepts, methodologies, and program implementation provide support for the success of biotechnology innovations and entrepreneurial ventures. In turn, innovation ideas are important to integrate back into the academic program to transform the academics into real world experiential learning. For example, a clinician with a product idea partners with the Navigating Regulatory Complexity in the Biotechnology Innovation course where students research and develop strategies and solutions relevant to bring the product to market.

Curriculum in this program is geared around experiential learning, taught by industry experts, with students producing real-world deliverables. Regulatory content can be overlaid with the content of the technical entrepreneurship course to create a single course. Alternatively, a series of courses can be offered as a certificate program or an academic track within a technology, science, management or dual degree program.

The program developed and described herein is a is a multifaceted and regulatory-centric approach intended to address unmet needs; giving students the ability to define, demonstrate, and strategically integrate the application of regulation to innovation, engineering research, technical product development, and biomedical entrepreneurship. The cycle of this part of the methodology is shown through the phases depicted on the right side of figure 3, as an integration of the methodology depicted in figure 2. Specifically, the curriculum framework is designed to mirror and complement the stages of the entrepreneurial lifecycle; from opportunity recognition through market entry, growth and liquidity. The series of courses are specific regulatory-centric courses that combine the regulated engineering and entrepreneurship activities that inform entrepreneurial actions. The topics and project outputs of one course can be input to the next course, although this is not necessary. For example, the series of courses may begin with *Navigating the Complexities of the Biotechnology Innovation*. In this course, students are presented with current, real world clinical problems, by physicians, for which there is no viable solution that addresses the unmet need. Students begin by forming a management teams and selecting which unfulfilled clinical need they will address. Then they research and engineer a design concept for an innovative technology solution for the clinical problem, and develop a commercialization strategy and plan for bringing that solution to the global market; constrained or informed by variable regulatory pathways and restrictions. Students employ learned and practiced concepts that span several regulated aspects of a regulatory strategy including: commercialization, execution, and sustainability of a regulated product.

In the next class, *Biotechnology Development*, students advance the solution developed as part of the regulatory strategy, into project planning and implementation, with the goal of bringing the invention forward, through the highly regulated design controls and good clinical practices, into patient care.

Biotechnology Business Control Systems, then, focuses on the regulated business operations necessary to ensure their specific technology is clinically viable, safe and effective. This course consists of regulation constrained subsystems and processes assembled for the purpose of reducing risk, reducing development time and enhancing product quality and operational sustainability of a medical device company. As part of a team, students apply Systems Engineering principles in a project based course to guide the design, interfacing, integration and assembly of control subsystems in the development of a regulated business management system-of-systems, according to global regulations. Each subsystem is created (on paper) through a set of requirements defined during top-down implementation and constructed simultaneously by different design teams that must work together to specify critical interfaces between the subsystems. Students verify these requirements through testing during mock implementation of the system design and must analyze the impact on product quality as a result of not accounting for subsystem interfaces.

Post Market Management then addresses regulatory topics related to the market entry and post market management activities of their technology and their system of business operations, such as: adoption of the medical intervention into routine care for the general public, sustained business operations, post market studies, product improvement, product obsolescence, business divestiture, and the like.

Creating a Biotechnology Enterprise, is a culmination of the series of in depth topics, or can be a single course, on its own, that introduces the same topics at a higher level. For example, it teaches students the concepts, skills and tools involved in success, and used to minimize failure, of highly regulated biotechnology initiatives. As part of a team, students demonstrate proficiency through creating, building, and commercializing their own simulated biotechnology enterprise (in the case of a single course on its own) or for the biotechnology they have developed through the series of courses. Real world, regulatory driven problems that influence their company are introduced throughout the semester. In both written and oral communications, teams evaluate and present their entrepreneurial actions in response to the particular problems. Students gain practical experience with biotechnology entrepreneurial ventures through active learning, solving complex challenges, and using the tools introduced in the course.

The series of courses are taught by an interdisciplinary team of highly qualified individuals from academia, industry, and the medical profession. Courses have an instructor of record, but all instructors guest lecture in courses and/or co-teach a course(s) to ensure proper coverage and to integrate interdisciplinary real world expertise into each course. Students that proceed through the entire series of courses receive a certification. This program, then could be appropriate as a certificate program, a track in a degree program such as in Engineering Management, or as a standalone professional course for non-college students.

In addition to filling the gap between what students learn and what they need to know to be successful in the regulated industry; the envisioned mission of the program is to reduce or remove global regulatory barriers and facilitate and accelerate the development and translation of scientific research discoveries and biomedical device innovations into commercially viable products, that can help people in need.

Key components of the program include:

- Academic Curriculum, Certifications, & Professional/Medical Outreach;
- Government, Industry, Global Universities & Professional Societies Collaborations & Partnerships;
- Regulatory and Translational Science Research, Collaborations, Services and Tools to expand the body of knowledge and help develop novel system solutions to regulatory, quality, safety, compliance and innovation challenges in the medical device industry.
- Medical Device & Healthcare Internship Opportunities & Career Services for students interested in the biomedical industry; and
- Networking & Mentorship to provide insight, direction, motivation, support and education that can best support chosen career paths and professional futures

Adapted from objectives defined by the Association for Graduate Regulatory Education, this program promotes five primary competency area objectives: Regulations, Quality & Operations, Clinical Investigations, Strategy, and Communications. Course content, has been developed in consultation or conjunction with medical device industry leaders, regulatory authorities and professional associations. As mentioned above, courses are taught by industry experts, regulators, or industry experienced and active academics; who bring years of practical experience from industry into the classroom, and keep content current to the global medical device and healthcare industries.

Real-world, experiential learning is a major component of this innovative interdisciplinary program and is realized through mentorship, internships and an academic curriculum that offers flexibility to allow for integration of synergistic university courses and additional areas of emphasis to support diverse career paths. A library of core content can be established that can then be tailored for different degree/certification programs, geographic regions, delivery methods, etc.

Action learning is enabled via close collaborations and project based opportunities with clinicians, medical device companies, regulatory agencies, and service organizations who support the program with capstone style industry projects, state of the art software tools, case studies and guest lectures. Hands-on assignments reflect current, real world deliverables in the medical device industry. The knowledge and experience gained from this program can provide immediate relevance and impact to: engineers, researchers, medical device innovators, entrepreneurs, and individuals who are currently employed in, or wish to enter the medical device industry; ensuring a tangible return on investment.

IV. Results, Conclusions, and Future Research

This program framework and details were reviewed with a multidisciplinary set of industry leaders from a variety of biomedical companies prior to course introduction. As well, three courses were introduced and piloted in a graduate engineering curriculum in

the spring of 2016, then another course in the fall of 2017. There has been overwhelmingly positive response from both industry and students. Strategically selected industry leaders have committed to partnering with this author as adjunct professors and guest lecturers to ensure students continue to receive only the most current education directly from an interdisciplinary set of highly experienced professionals. Likewise, a number of students have received internships, as well as having obtained jobs upon graduation, in the biomedical industry in the Quality and Regulatory professions; attributing their success specifically to these courses.

The methodology for developing this program is unique and is aimed at cross training, equipping, developing and preparing the next generation of engineers, entrepreneurs and innovators, with the necessary understanding to effectively address the increased complexity of the modern regulatory landscape. There is a need for further research in the broader implementation of this program and in the further development of the methodology for biotechnology ventures. Likewise, there is the need for future research in other regulated areas. Consequently, a method could be developed for each of these methodologies and, possibly, development of a universal methodology for regulated ventures, in general.

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