A Methodology to Integrate Regulatory Expertise, Research and Education to Accelerate Biomedical Device Translation

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ABSTRACT

The aging population, new healthcare needs, and people living longer are driving an unmet clinical need for biomedical research and development of innovative medical devices. Academic research and development is a key component of biomedical R&D. Academic scientists and engineers have considerable ability to contribute to addressing the unmet clinical need. However, turning basic research into clinical interventions, such as medical devices, that improve the health of individuals, is exceptionally difficult. Device development and/or use of these devices in human clinical studies, even if for early feasibility studies, is highly regulated, requiring a unique knowledge base that is often lacking in academia. For successful regulated device development, and subsequent regulatory approval, researchers need access to tools, expertise and resources that can help simplify and accelerate an often complex and lengthy regulatory pathway while providing for patient safety and regulatory compliance. Therefore, it is necessary to integrate the use of regulatory and quality consulting and expertise into the translational process for taking scientific research into clinical research into usable innovation. Bringing together this type of synergistic relationship to advance research offers value to the researcher, the regulatory consultant, the students, and the patient population for which the technology was developed or will be used. This paper will discuss a model for an integrated biotechnology focused clinical research translational center that integrates research, regulatory, compliance, quality, and academics.

Keywords: Higher Education, Engineering, Regulatory Science, Medical Device, Translation.

INTRODUCTION AND NEED

According to the National Institutes of Health, Office of Extramural Research, NIH is the largest federal funder of clinical trials in the United States, investing $3 billion per year in clinical research [1]. In the case of research using biomedical technology intended for use as a medical intervention in humans, requirements from funding agencies, such as NIH, are swinging the pendulum beyond the science and into human clinical trials. However, technology development through research is a long, costly, and risky endeavor. Currently, "a novel drug, a device, or other medical intervention takes about 14 years and $2 billion to develop, with a failure rate exceeding 95%" [2]. Where basic research and feasibility analysis are not highly regulated, if at all, the movement to the use of technology in human studies, even if for early feasibility studies, becomes more highly regulated, therefore requiring a unique knowledge base that is often lacking in academia. Realizing this, NIH has launched a series of trainings for researchers to help them understand the requirements for clinical trials, such as good clinical practices, institutional review boards, clinical protocols, and clinical trial registration and results submission [3]. While this is noteworthy, it does not address other complex regulatory requirements necessary to achieve product quality and FDA approval for the human use of an investigational device, such as: quality, risk management, design controls, regulatory pre-submissions, and final regulatory submissions. In fact, NIH has observed that increased regulatory burdens, among other barriers, and the lack of know-how to address these regulatory burdens, are a common challenge for researchers in clinical and translational research [4]. This can delay the development of new devices for patients in need.

For successful device development, and approval for clinical investigational human studies, researchers need access to tools, expertise and resources that can help simplify and expedite an often lengthy regulatory process while providing for patient safety and regulatory compliance. Therefore, it is necessary to integrate the use of regulatory and quality consulting into biomedical research to translate basic scientific research, into clinical research, and on to usable innovation. Bringing together this type of synergistic relationship, to advance research, offers value to the researcher, the regulatory consultant, the students, and the patient population for which the technology was developed.

The aging population, new healthcare needs, and people living longer are driving an unmet clinical need for biomedical research and development of innovative medical devices. Academic research and development, as well as research performed by research labs and industry, are a key component of biomedical R&D. Academic scientists and engineers conduct the bulk of US basic research, and therefore have the greatest ability to significantly contribute to addressing the unmet clinical need [5]. However, turning basic research into clinical interventions, such as medical devices, that improve the health of individuals, is exceptionally difficult.

NIH has demonstrated their strong commitment to convert more of the research it supports into tangible products. They have launched such programs and initiatives as the Clinical and Translational Science Awards and the Research Evaluation and Commercialization Hubs (REACH), among many others [6].

These initiatives are intended to provide tools to help researchers work through common barriers such as the regulatory burdens.

Considering NIH's $3 billion per year investment in clinical research [7], the question arises, then, as to why <5% of innovative therapies actually become clinically available for their intended population. This answer may be due, in part, to it still being too early to see the impact of these NIH programs on their overall translation metrics.

Another reason may be that, although these training programs and initiatives are extremely noteworthy, on the broad scale, for providing the knowledge and skills about *what* to do for translation, they cannot reasonably be expected to provide variable researchers the necessary focused and detailed implementation instruction for *how* to address their precise, complex and unique regulatory issues.

Specifically, regulated 'it-depends' deliverables are necessary to achieve device specific product quality and FDA approval for the conduct of human investigational device studies. Some of these specific deliverables pertain to the practice of regulation in quality, risk management, design controls, and regulatory and standards compliance testing. Hence, there is still a need to localize the regulatory and quality tools, expertise and resources within translational research to help simplify and expedite the lengthy and complicated regulatory process, while providing for patient safety and regulatory compliance.

This research develops a model and methodology for a synergistic relationship between the research domain, the regulatory domain, and the academic domain for a vertically integrated, biotechnology focused clinical research translational center that addresses barriers to medical device translation and accelerates the delivery of innovative biotechnology.

BACKGROUND

In academic research, translation is the process of turning basic research into clinical interventions, such as medical devices, that improve the health of individuals and the public. NIH describes this process with five stages of the Translational Science Continuum as depicted in figure 1: Basic Research, Pre-Clinical Research, Clinical Research, Clinical Implementation, and Public Health. [8]

Figure 1 Translational Science Continuum Stages

Traditionally, clinical research has been the predecessor to technology transfer to industry. Bringing research through the continuum to human clinical study shifts the traditional research role towards the new product development role played, more so, by industry. There are a number of industry models that describe the stages of new product development. For example, the Product Development Management Association describes the stages of a new product development process to include: Scoping, Building the Business Case, Development, Testing and Validation, Launch [9].

New product development of a biomedical innovation intended for human use includes a stage that is not common for an unregulated product, and that is the regulatory review stage. The US FDA has identified seven stages necessary to bring a product to market through the variable regulatory pathways, as depicted in figure 2. These include: Discover & Ideation, Invention & Prototyping, Pre-clinical, Clinical, Regulatory Decision & Product Launch, and Post-Market Monitoring [10]. The operations and activities that propel the technology development through the stages of new product development for this type of product are highly regulated. Also, the practice of regulations throughout the stages of the product development lifecycle is highly structured and provides a roadmap for device development. Experienced interdisciplinary project team members, e.g. from departments of Science, Clinical Affairs, Engineering, Manufacturing, Quality, Regulatory, among others, as well as service providers such as certified regulatory testing services, all have a role in satisfying the regulated operations necessary to bring a product to market.

Figure 2 New Product Development Stages

The challenge of a center with the mission to facilitate medical device translation is to strike the balance between the flexibility of the nonregulated research operations and the structure, rigor and expertise of the regulated new product development process seen in the biomedical industry.

INTEGRATED SYNERGISTIC MODEL AND METHODOLOGY

Figure 3 shows a model for bringing clinical translational research, regulatory, quality and compliance services and tools together into a single, synergistic vision for a Translational Center. This framework leverages an industry product development process, modifying and scaling it to accommodate for the needs of a research endeavor. This results in a model infrastructure to propel early-stage medical device projects forward and to engage and educate students, researchers, engineers and medical device inventors to be partners in transforming research discoveries into clinically viable medical devices, and even entrepreneurial ventures.

This Center model is comprised of a synergistic series of domains, or areas, working together to achieve an integrated balance of operations. Working from the top down, there is a Translational Research domain that evolves from basic science to clinical implementation of a biomedical technology. The Translational Research Domain leads the biomedical research

programs and is focused on addressing unmet clinical needs through transformative investigational device development and early feasibility or pilot clinical trials. Projects that enter the Center are ones with technologies that are poised for proof of concept, prototype development, clinical feasibility testing, product development, and regulatory submission.

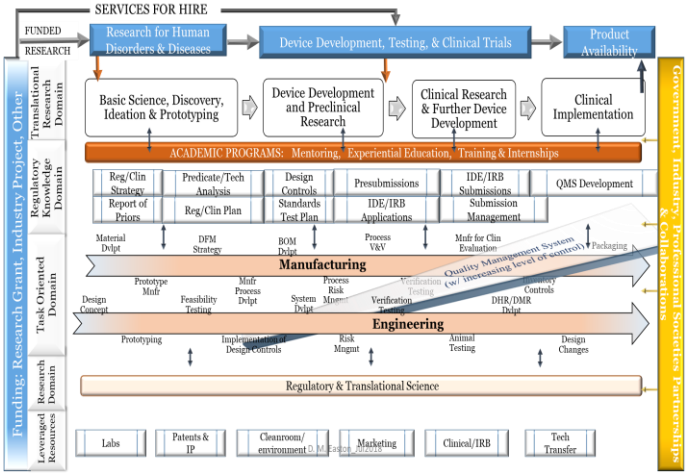

Figure 3 Integrated, Synergistic Translational Center Model

Central to the model, and integrated with the Translational Research domain is the Regulatory Knowledge domain. Where other centers focus on a specific research, this model is uniquely driven by regulatory-centric services, operations, strategic partnerships and collaborations associated with translational research and regulated product development. Operations of the Center benefit from strategic partnerships and collaborations that contribute to its vertically integrated infrastructure. They are critical to the Center's success and operational optimization. Collaborations and partnerships may operate as part of a sponsored research agreement, a collaborative research agreement, or participants can directly provide gifts or services in kind. These entities may include Government, Industry, Academic, and Professional Society Collaborations. These collaborations and partnerships reduce costs and augment Center operations in mutually beneficial relationships. For example, an industry certification test house could enter a partnership framework through a strategic collaborative research agreement that does not include financial resources, as each party is bringing something to the relationship. An example of this type of service exchange could be as represented below:

- Industry Partner provides:
  - Preclinical testing services (applicable to the Partner's area of expertise) for translational products developed through the Center
  - Training/Education, for example:
    - Electrical Safety Requirements and Testing – Medical Equipment and other systems,
    - EMC Requirements and Testing - Medical Equipment and other systems,
    - Risk Management as applied to Medical Devices and compliance with standards,
    - Interoperability and Coexistence of Medical Devices in Hospital and Home Settings,
    - Regulatory Requirements for Market Entry in US, EU, and other interested countries,
  - Subject Matter Expertise for periodic consultation on other translational projects, and
  - Guest Lectures and student networking, internship, and employment opportunities.
- Center provides:
  - Faculty partners to engage in Public-Private Joint research,
  - Co-op and Interns as part-time company employees,
  - Academic Program graduates as potential fulltime company employees or subcontracted consultants upon graduation,
  - Subject Matter Experts, in the specific fields of research at the Center, that provide input and advice on Industry Partner projects,
  - Joint publications,
  - Marketing, advertising and promotion of Industry partner, and
  - Business feeders with startups and companies engaged in research and product development with the Center.

Other examples of mutually beneficial strategic partnerships and collaborations may include:

- Collaboration on course content in the Academic Program and integration of company products into course case studies and projects: e.g. Design Controls & Risk Management, integration of Human Factors and usability in design, Quality Systems and Compliance, Clinical and Regulatory Strategy, etc.,
- Student Internships - Internship opportunities for students who would work remotely to complete a specific project under company direction and guidance,
- Sponsored research agreements – Under an approved proposal. Graduate engineering student(s) perform defined work over a defined period of time. Collaborative publications throughout research,
- Collaborative research agreements – Company and University seek funding together to perform joint research,
- Industry partner provides a device verification or validation protocol to be implemented in a course, giving participants "practical experience", and the Industry partner an outsourcing option for testing, as well as, a potential employee pool with experience on their product,
- Industry partner provides state of the art software tools to the Center for use in the generation of Case Studies.

Center & Industry partner co-author case studies publication. Industry partner can do an onsite training of the product to key faculty within the Center and help guide first time use. Then, the Center utilizes software with translational projects as a method of optimization and publishes the results of the optimization effort. This could be generated as part of a sponsored research agreement. Additionally, software can be utilized in courses to provide a unique opportunity for participants to use new, cutting edge tools, developed for medical devices, which would be otherwise unavailable to them. The Industry partner gets participants who have experience and interest in their product.

- Co-Publications, e.g. under an umbrella of accelerated innovation, translation or product development optimization, etc.
- Industry partner guest lecture in Courses,
- Advertising and promotion, e.g. posting collaboration on web sites,
- Collaboration on Industry partner product development
- Broadened networking opportunities for both parties

Finally, systematic engagement in mutually beneficial relationships with existing University functions and resources, such as Technology Transfer, Patenting and Intellectual Property, Marketing, or other resources, offers an important element to the optimization of the Center operations.

A critical part of the Regulatory Knowledge domain, and strategically integrated with the Center operations, is an academic framework, such as that described in a Biodevelopment program [11]. The Academic program is intended to foster an active learning environment while helping to reduce operational costs of the Center. Similar to Biodevelopment, this academic element of the model aims to provide for mentorship, internships, research collaborations and academic tracks that span regulatory topics across the biomedical product development lifecycle. The curriculums in this program are geared around experiential learning, taught by industry experts/consultants, with students producing real-world deliverables. The knowledge and experience gained from this type of program provides immediate relevance and impact to the next generation of engineers, researchers, medical device innovators, entrepreneurs, and individuals who are currently employed in, or wish to enter the medical device industry, along variable career pathways. Students have the opportunity to define, demonstrate, and strategically integrate the application of regulation to innovation, translational research, technical product development, and biomedical entrepreneurship. This body of knowledge will prepare and equip students with the understanding and know-how to efficiently and effectively apply the medical device regulations, to multidisciplinary practice, through critical stages of the translational science continuum, the new product development lifecycle, and the business of medical devices as a whole.

Next is the Task Oriented domain. The Task Oriented domain provides necessary engineering and manufacturing regulated deliverables for design and small-scale manufacturing of clinical devices, as guided by the collaboration with the Regulatory Knowledge domain. The Task Oriented domain consists of interdisciplinary functions that partner and integrate with resources from the Regulatory Knowledge domain to form the interdisciplinary team necessary for regulated device development, as is common in industry-based product development. The Engineering function in the Task Oriented domain engages students and participants within the Academic programs to assist with translational research and device development by de-risking the advanced medical technology as part of an engineering curriculum. This is done by building devices and completing preclinical testing under regulated design controls to provide the necessary design input, design output, and verification and validation deliverables to support translation. These domain tasks can include: device prototyping, formal design, specification development, drawings, schematics, coding, verification testing protocols and test reports, risk management activities, etc. Often times, innovative devices require innovative materials and/or manufacturing. The Manufacturing function in the Task Oriented domain serves innovators, entrepreneurs, students and faculty with the research, development, testing and small-scale production of advanced technology, being developed through the Center, for use in investigational clinical trials. This also can engage students and participants to provide certain regulated manufacturing engineering deliverables such as: a design for manufacturability strategy, development of the manufacturing process, process validations, generation of device history records, etc.

All domains operate under a Quality Management System that establishes, streamlines and controls the Center infrastructure, costs and operations. A Quality Management System is a required regulatory control system applicable to medical devices. A flexible Quality Management System, with increasing levels of controls as the project progresses through the product development stages, and leveraging established university resources, is a valuable tool for the Center. Whether certified or not, it plays a key role in the product development and manufacturing requirements. This type of operating system will streamline and control Center operations, align expectations & offer or reinforce legitimacy of Center deliverables to variable stakeholders. It will also reduce operational costs in individual translational projects and Center operations by establishing ready-made processes that can be applied across variable projects, such as design controls. Implementation and management of the Quality Management System also provides consulting and student internship opportunities for those interested in this career pathway.

Finally, the Research domain is intended to stimulate advances in the translational and regulatory science body of knowledge and develop novel system solutions to regulatory, quality, safety, and compliance challenges. Research opportunities for students are generally lacking in regulatory science, quality, safety, compliance, and translational science. The Research domain in this model gives students and participants a chance to gain valuable experience in solving significant problems that face the medical device industry.

Together, these domains establish this vertically integrated and regulatory service centric Translational Research Center. This integrated synergistic model is meant to rapidly address translational barriers in innovative ways. It provides the industry level regulatory knowledge and expertise to guide and satisfy regulated engineering, product development, and manufacturing tasks unique to the translational products being developed. Additionally, it provides regulatory affairs, clinical,

and quality services and tools necessary to deliver these products to patients. The interdisciplinary regulated activities across these domains are highly collaborative and work together to reduce or remove complications across the translational science continuum – from bench to bedside.

In this model, Center funding can initiate with a single or multi-phased funded translational research project or with the commission of: clinical, quality or regulatory services, training, or testing for investigational devices or new indications. For example, a small startup with limited headcount may want to hire the center to generate certain regulatory deliverables common and necessary for a medical device company such as the development of: A Quality Management System, a Regulatory Strategy, an FDA submission, or specific documents that must be included in a regulatory submission, such as a Report of Priors or a Device Evaluation Strategy. The charge for these services can be significantly reduced compared to large organizations with similar services, and it is certainly less expensive than a startup hiring full time resources within their small company.

Resources within the Center, such as from student internships and shared regulatory, clinical, or quality consultants, that don't require the overhead expense of permanent employees, would provide these services. These resources would be funded, in large part, by these commissioned projects, as well as through research grants as a shared service, as needed. Alternatively, or additionally, a more innovative approach would be to integrate the desired commissioned deliverable as a course project. For example, a small startup that needs a quality management system would commission the services of the center. This, then would be the focus of a real-world project, in the Design and Development of Integrated Quality Management Systems course. Under the direction of a highly qualified instructor, one with significant real-world experience such as: a consultant, industry adjunct, or experienced academic; and tight collaboration with the client, students get the real-world experiential learning they want, and the client gets the deliverable they desire at a small fraction of the typical cost. This interaction can work for a variety of regulated work products.

CONCLUSIONS AND FUTURE RESEARCH

As mentioned previously, the Regulatory Knowledge domain is central to the entire model and drives the regulatory services, regulatory-centric academic program and the Center operations, collaborations and partnerships in support of the Translational Research domain objectives, or commissioned regulated activities. The fundamental objective of this domain is to strategically support innovators, entrepreneurs, students and faculty. This support will facilitate and accelerate the regulated development of innovative products and the performance of clinical studies by addressing some of the regulatory barriers that impede the translation process for a regulated biomedical product. It accomplishes this through the creation, implementation and provision of regulatory and operational products, services, guidance and tools necessary to deliver these new technologies to patients; with an emphasis on novel system solutions to clinical, regulatory, quality, safety, and compliance challenges in the medical device translational continuum. In addition to commissioned activities and projects, this domain can support research requests for proposals, as well as grant milestones and deliverables. These specific tasks can be customized and augmented for a Center's specific area of focus, as desired.

This model is an interdisciplinary, synergistic model that applies modified and scaled business discipline specific to product development in the regulated medical device industry. Applying this type of discipline to advanced research de-risks and accelerates university-based translational research projects. The translation is accelerated by collaborating with regulatory and clinical consultants experienced with commercial business operations and product-development practices from the biomedical industry. Using these resources to provide flexible, risk based early engagement of regulated activities, such as design controls and regulatory strategy, eliminates gaps and bottlenecks in the earliest stages of the new product development process – thereby accelerating the translation of Center-supported discoveries and technologies into new products.

There are many innovative differences in this center model. However, a key difference is that the underlying focus of the model is on the regulated operational principles of translation and translational science; not on the independent translation of a specific device for a specific research. This focus lends itself to better strategic partnerships, collaborations, processes and tools appropriate to the success of a Translational Center model. This approach establishes and maintains a more collaborative and harmonized operational infrastructure to consistently drive early-stage clinical research projects forward. It also engages and educates students, researchers and medical device inventors to be synergistic partners in transforming their discoveries into high-impact advances in patient care. And, hopefully, it brings new products and devices to market in a more expeditious, safe, and cost-effective manner, for patients in need.

This model focuses on the regulated biomedical discipline. However, regulations, and more so, the *practice* of regulation, is applicable to a large variety of disciplines. Hence there is a need to research and develop a core framework that can be applicable to removing regulatory barriers in all regulated disciplines.

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