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PERSPECTIVE

The New (Challenging) Role of Academia in Biomaterial Translational Research and Medical Device Development

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Abstract With the ever-changing landscape of translational research, the medical device and pharmaceutical industries increasingly license technologies with the added value of clinical and/or pre-clinical data rather than those in earlier stages of development. Universities have the potential to fill the gap in product development from academic laboratories through enhanced student training and increased implementation of some development and manufacturing activities that are traditionally found only in the private sector. A development roadmap is described from initial product feasibility through commercialization in the context of efficient development practices. The specific challenges in the design and development of biomaterial-based medical devices are described in the context of this development path with an emphasis on unique challenges for academic laboratories.

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1 The Changing Landscape of Translational Research in Medical Devices and Drugs

Translation of novel medical technologies from academic laboratories to the market has undergone a major shift over the past several years. Changes in this landscape have moved commercial licensing and intellectual property transfer deeper into the product development timeline. This has a profound implication for the role of academic institutions and researchers. Medical device and pharmaceutical industries are experiencing increased regulatory scrutiny with initiatives focused on comparative efficacy research and the sentinel initiative, which bolsters increased product oversight throughout development [1]. These initiatives are adding value to potential products by ensuring greater consumer safety. However, they also strain this increasingly cost-sensitive and risk-averse industry. The development path for an idea to a medical product is typically based on multiple factors including market trends, tendencies of the industry, capitalization, and regulatory requirements [2, 3]. Figure 1 highlights the critical path in the development of an idea to a product and this includes: invention and patent application, basic research, product design and development, manufacturing, pre-clinical and clinical testing, regulatory review, and commercialization. Throughout this path, windows of opportunity exist for licensing so that the inventor does not carry the technology entirely up to and through product commercialization. Licensing refers to the process in which the owner of a patent or copyright grants another entity the rights to use the patent and in return receives royalties on product sales

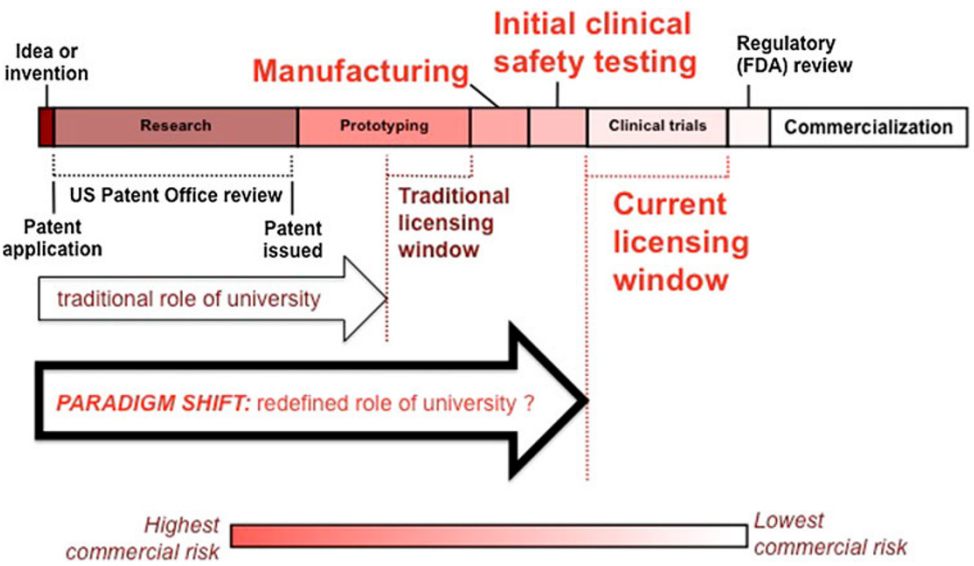

Fig. 1 General development path for translational medicine with a shift in the window of opportunity for licensing intellectual property

or other compensation. In the past, companies have been willing to license technology while it was still in the research phase or early product design. However, in recent years, companies and venture capital groups have focused on reducing their risks by requiring pre-clinical data and may even desire human clinical data prior to investment. Value-added pieces such as design documentation, manufacturing protocols, or clinical data often demonstrate that reduced risk. Therefore, the pressure is on the inventors to engage in product development through manufacturing and clinical assessment.

The shift in research goals and development efforts prior to licensing begs two key questions: (1) who can/should fund the process of carrying inventions through manufacturing, regulatory filing, pre-clinical and clinical safety trials, and (2) who is best equipped to do so? Ideas that begin in larger corporations often start with the capital to usher inventions through these processes. But in many industries, discovery and development efforts are consistently in the risk of being eliminated from the operational budget. Funding agencies for academia typically support mechanistic and hypothesis-driven research (i.e., high commercial risk) so have not been traditionally involved in activities such as product manufacturing or pre-clinical or clinical trials. However, major granting agencies have recently initiated pilot programs, such as the Clinical and Translational Science Awards (CTSA) and the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) in the US, to support translational efforts in academia in order to encourage newer technologies to enter the market. Universities serve a key role in society by educating students in nearly all areas of study and also facilitating research and training in almost as many disciplines. However, applied engineering, basic science research, and medical practice are not traditionally grouped together to confront the challenges of translational medicine. Manufacturing, regulatory filing, and clinical trials require novel partnerships across these disciplines. Additionally, expertise in manufacturing and regulatory filing is often acquired through on-the-job training in industrial or corporate settings. Therefore, bringing these skills into academia requires partnership with industry experts and recruitment of faculty with industry-focused experience. But then the overall educational mission would need to be reassessed. Graduate training in physical and biological sciences traditionally involves formulating testable hypotheses then evaluating through rigorous experimental design. To modify this training paradigm by including goal-oriented product development may be controversial. But this dilemma does demonstrate the challenge of finding a new balance amongst effective student training for the workforce, societal needs, and funding trends.

2 Key Product Development Challenges in Academia

Organization and management are essential in device development, because these initiatives require larger teams of highly diversified individuals. However, highly structured and regulated processes, which include major strategies for product and possibly business development, are not common in academic laboratories. The following resources may be used to help guide scientists and engineers who are new to development. Piezsch et al. [4] describe a useful structure for managing device development from concept selection to post-market surveillance in accordance with regulations imposed by the International

Standards Organization and the United States Food and Drug Administration. This development guide details five sequential phases: (1) Initiation/opportunity and risk analysis, (2) formulation/concept and feasibility phase, (3) design and development/verification & validation phase, (4) final validation/product launch preparation phase, (5) and product launch and post-launch assessment. Additionally, multiple strategies for intellectual property, research and development, regulatory filing, and clinical approaches have been effectively summarized by Zenios, Makower, and Yock [5]. These published resources may be used to help academic scientists and engineers manage and organize key steps of development. Another component in product development is cost analysis of new medical device and/or drug technology and the efficacy thereof in the eventual clinical success. There are multiple examples in drugs and devices where the significant increase in cost correlated to only a marginal increase in extended life expectancy as a success benchmark. While this is not often considered in basic science laboratories, such cost-effective analyses regularly drive the decision making process in product development in the private sector.

Material synthesis and manufacturing introduce many technical design challenges that are often unfamiliar to academic researchers but are part of the critical path in product development. Some of these include scale-up, equipment limitations, sterile processes, and endotoxin management. These challenges play a major role in planning and budgeting as well. Understanding the complexity of these challenges can assist in process design toward a greater success in navigating the product development process. For example, synthesis scales in product development can be multiple orders of magnitude larger than that required for most basic research studies. Efficient scale-up in production requires incremental increases in the amount of starting products for each synthesis then followed by extensive characterization to confirm verification parameters. This approach may help to identify issues related to supplier quantities, reagent efficiencies, and/or equipment limitations. Targeted cost-benefit analysis can help to determine the utility of either scaling-up synthetic equipment or dedicating more labor time. Assessing development goals may also inform scaling activities. For example, more attention may be paid to process efficiency if the goal is to build a company rather than out-licensing to increase process efficiency. Contract manufacturing organizations (CMO) may provide assistance to overcome equipment limitations and scale-up issues, particularly when good manufacturing practice (GMP) manufacturing and packaging conditions are required. Identifying a suitable partner amongst the myriad CMOs can be a daunting effort. A prioritized list of CMO criteria would help to hone in on the ideal partner. Considerations may include: specialized equipment capabilities for the material in development, willingness to accommodate the scale of the project, assist in process development including workflow and packaging, analytical capability which can assist in product verification, downstream packaging and labeling that require a sterile environment with GMP validation that are rare in academic settings, cost, effective communication and transportation.

Sterility is one of the most critical considerations for patient safety and product success. Although considered by academic researchers, it may not be at the level and rigor required by regulatory agencies. Sterilization can be disruptive to synthetic processes or can modify the final product to an extent that inhibits its end-stage use. Considering sterilization very early on in the process design would minimize these disruptions. Filtration, electron-beam treatment, λ-irradiation treatment, or ethylene oxide exposure are all common techniques which can be built into the manufacturing process. Microbial content alone is not the only immunologic threat to patients. Microbial endotoxin levels must be closely monitored and mitigated to reduce the potential for untoward device-related immune response and complications. Regulatory agencies have strict guidelines for this. Animal-derived materials such as collagen are notorious for high endotoxin content that is difficult to remove.

The aforementioned topics are starting to be incorporated into classroom education at undergraduate and graduate levels in institutions such as Stanford (http://www.stanford.edu/group/biodesign/bme-idea//meetings/10-11/) and University of Wisconsin—Madison. This trend is expected to increase as universities take on a more active role in medical product development.

3 Conclusion

The licensing of intellectual property in medical devices and drugs is occurring much later in the product development path. Universities are positioned to tackle challenges in product development such as manufacturing, pre-clinical and clinical safety testing as a part of the educational and research mission. Appreciation and understanding of the basic critical path of initiation, formulation, design and development, final validation, and product launch should be incorporated into undergraduate and graduate education. Understanding key challenges in this development-to-product process will also help universities in assessing its research mission, funding priority, and patent portfolio.

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