INSIDER VIEWS

What Is the Greatest Regulatory Challenge in the Translation of Biomaterials to the Clinic?

Glenn D. Prestwich,[1]* Sangeeta Bhatia,[2] Christopher K. Breuer,[3] Shannon L. M. Dahl,[4] Chris Mason,[5] Richard McFarland,[6] David J. McQuillan,[4] Jonathan Sackner-Bernstein,[7] Jeffrey Schox,[8] William E. Tente,[4] Alan Trounson[9]

Leaders in the field comment on what they perceive to be the greatest barriers to biomaterial translation.

FACE THE STRANGE

So goes the proverb, "Where there's a will, there's a way." But when translating biomaterials to the clinic, the "way" isn't always so clear. Moving biomaterial-based products from the bench to the clinic takes more than a will; it takes regulatory approval, too.

Regulatory hurdles for biomaterials that use clinically approved natural or synthetic scaffolds can be lower than those for new innovations. Under the 510(k) process at the U.S. Food and Drug Administration (FDA), devices that are cleared as "substantially equivalent" to an existing device can be marketed quickly. Conversely, new materials have to prove biocompatibility with human tissues, which takes several additional years of preclinical (animal) studies. Translation: More time, more money.

The challenge is how to innovate and translate safe, novel materials that address unmet clinical needs in the shortest amount of time possible. To identify some common bottlenecks, we asked nine biomaterials experts who are thought-leaders in one or more sectors—industry, nonprofit, academia, clinical, intellectual property, venture capital, and regulation—a seemingly straightforward question: "What is the biggest challenge in moving biomaterials into the clinic?" As you will see, their answers are complex, but one thing is clear: Translation is a convoluted path.

—**Megan Frisk and Kelly LaMarco**
Science Translational Medicine

UNCERTAINTY PRINCIPLE

Christopher K. Breuer, M.D.
Deputy Vice Chair of Research and Director, Tissue Engineering Program, Ohio State University. E-mail: christopher.breuer@nationwidechildrens.org

Barney the Friendly Dinosaur was a popular children's television show in the 1990s. Barney had the unique ability to captivate young children, who would remain glued to the television, analyzing the purple dinosaur's every move. But, when adults watched the show, they were perplexed by what the children found so interesting about this anthropomorphic *Tyrannosaurus rex*. The answer is simple: familiarity and predictability. After watching even a single episode, children became so familiar with Barney that they knew what he was going to do before he did it. As human beings, we are drawn to and find comfort in a world that is predictable. Unfortunately, our ability to predict the future in the real world is less accurate than in Barney's world.

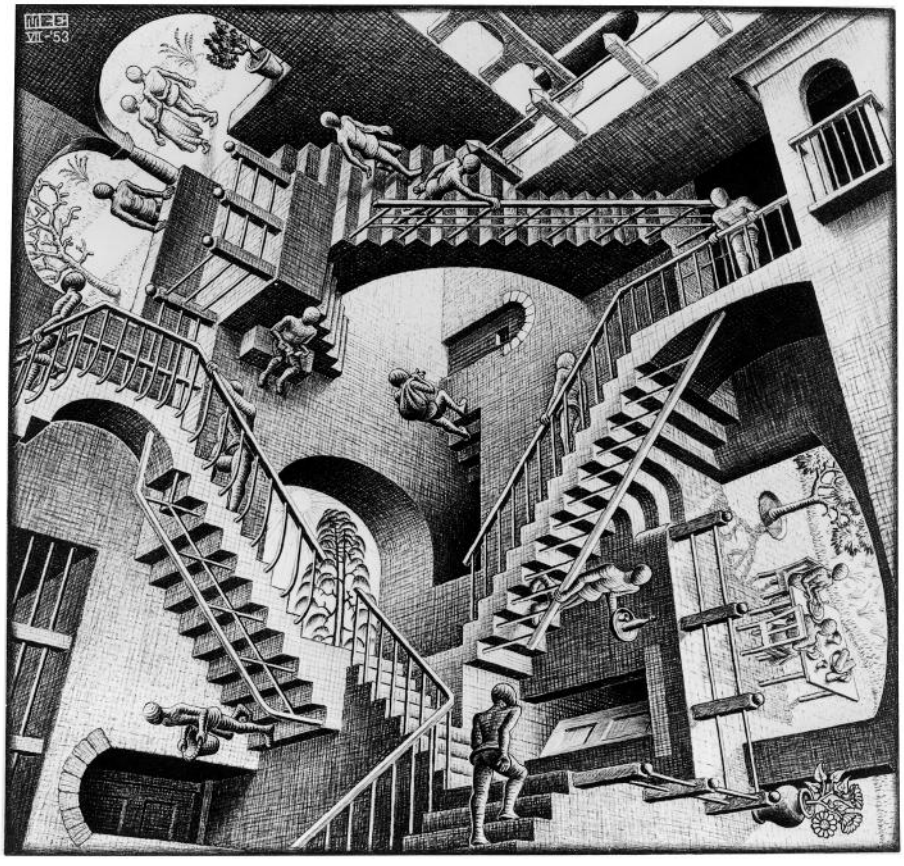
Which leads us to one of the greatest regulatory challenges in translational research: the ability to accurately predict, from preclinical data, the human health risks associated with a new product. This exercise is at best an imperfect science and is particularly challenging for new biomaterials or other novel technologies for which there are not well-established, standardized metrics for testing safety. The limitations of established preclinical studies—which include theoretical modeling, in vitro cell-based assays, and investigations in animal disease models—to recapitulate and accurately predict the safety and efficacy of new products intended for human use have been well documented. Preclinical studies provide valuable data that can help scientists estimate starting doses for clinical trials and predict potential product-related safety issues. But ultimately, the performance of translational research requires a leap of faith because preclinical investigation cannot accurately predict every safety issue related to a product; there is always the risk of unanticipated adverse events.

This uncertainty is balanced in part by the use of multiple preclinical model systems in an attempt to improve the accuracy of predictions; however, doubling up does not eliminate the uncertainty problem, which is compounded by what I refer to as the Barney phenomenon: an overreliance on a battery of familiar, well-established, but sometimes clinically less relevant investigations that are frequently required before performance of clinical studies. Substitution of well-established but clinically less relevant model systems with more refined and clinically relevant model systems offers the ability to improve predictability with the use of fewer preclinical studies. For example, in our own efforts to develop a tissue-engineered vascular graft (TEVG), we adhered to standard guidelines and performed costly, Good Laboratory Practice (GLP) studies to evaluate the inflammatory response to the TEVG as subcutaneous implants in a variety of small-animal models instead of evaluating the inflammatory response of our grafts in the circulatory system, where they would ultimately be used.

Although these studies provide a baseline level of data in support of the safety of our product in human subjects, I wonder how useful the data generated were in successfully predicting and preventing us from jeopardizing the safety of the patients? In fact, I would argue that evaluation of the inflammatory response to a graft implanted in the subcutaneous space has little relevance to its inflammatory response in the circulatory system. We have subsequently developed and validated new, more refined animal models that have enabled us to evaluate the inflammatory response of our grafts in the circulatory system. These more clinically relevant models have helped us to further investigate the primary mode of action of our TEVGs and have provided clinical and pathophysiological insights that will guide us toward improvements in the safety and efficacy of our product, aid us in the design of clinical trial protocols, help us to develop better quality-control and quality-

[1]Department of Medicine, University of Utah, Salt Lake City, UT 84108, USA. [2]Koch Institute for Integrative Cancer Research and Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. [3]Center for Regenerative Medicine and Cell-Based Therapies, Wexner Medical Center, Nationwide Children's Hospital, Ohio State University, Columbus, OH 43205, USA. [4]Humacyte, 7020 Kit Creek Road, Suite 110, Research Triangle Park, NC 27709, USA. [5]Advanced Centre for Biochemical Engineering, University College London, London WC1E 6BT, UK. [6]Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Rockville, MD 20852, USA. [7]Neostem, New York, NY 10170, USA. [8]Schox PLC, San Francisco, CA 94107, USA. [9]California Institute for Regenerative Medicine, San Francisco, CA 94107, USA.

*Corresponding author. E-mail: glenn.prestwich@pharm.utah.edu



Translational labyrinth. Biomaterials translation mounts many obstacles, including time, money, innovation, and safety. Although the paths and outcomes are uncertain, the ultimate goal is not: improving human health.

assurance measures, and identify new biomarkers for monitoring the function of the TEVG.

Investigators and regulators share the same goal: to ensure the safety and promote the welfare of our patients. The performance of translational research requires a careful evaluation of the degree of risk versus the potential benefit to the recipient. Efforts to develop more relevant preclinical models rather than a persistent attachment to previously used, well-established, but clinically less relevant safety assays will accelerate and improve the process of bringing new technologies from the bench to the clinic. And that is a comforting thought.

NATURAL SELECTION AGAINST NEW BIOMATERIALS?

Alan Trounson, Ph.D.
President, California Institute for Regenerative Medicine (CIRM). E-mail: atrounson@cirm.ca.gov

The clinical translation of complex biologically responsive materials is a serious regulatory challenge in the biomaterials field. The use of biomaterials in regenerative medicine is in the early stages of its evolution to enable efficient stem cell differentiation and maturation of biological functions of the products. Bioresponsive materials and gels such as self-assembling nanofibers can enhance the maturation of therapeutic cells—commonly, progenitor cells that give rise to selective tissue types—and integration of the differentiated cells into specific tissues or body regions. In addition to cells, these biomaterials may also be further modified to deliver growth factors or other bioactive molecules. The materials generally remain intact in the body only long enough to enable functional integration of the transplanted donor cells with host tissues before biodegrading at a predetermined rate.

Relative to purely synthetic or purely bioderived materials, bioresponsive materials face additional hurdles on the way to regulatory approval. First, these complex entities may be treated as combination products and require regulatory approval of the material or device as well as the cellular components for all aspects of safety and performance. Second, unlike scaffolds or matrix materials that are stable in the body, which are themselves challenging when it comes to obtaining regulatory approval, bioresponsive materials may need to demonstrate additional safety and efficacy properties, such as appropriate gene expression and signaling for both donor-cell lineage maturation and host-tissue receptivity; cell and tissue integration without causing injuries (such as inflammation, foreign-body response, fibrosis, or rejection); safety of the degradation products; and longevity of therapeutic benefit. These requirements are all in addition to independent cell-product testing and take substantial additional resources to address.

Biotechnology companies prefer to develop cell products in approved materials rather than to take a new material and cell product forward, even if the new approach has the potential to be more effective clinically. Industry may even avoid the use of a material with a cellular product; for example, embryonic stem cell–derived retinal pigmented epithelial cells are in clinical trials for transplantation without an adhering scaffold that could ensure natural monolayer structure and function (NCT01344993). In the case of type 1 diabetes, companies with pending clinical trials prefer to deliver pancreatic β-islet progenitor cells housed in already-tested capsules rather than use new bioresponsive materials (such as self-assembling biopolymers) in order to avoid destruction of the cells by the recipient's immune system.

To enable their survival, either biomaterials or the regulatory process must evolve: Scientists may have to simplify bioreactive materials and cell composites, or regulatory agencies will need to make changes in the approval process to make the environment more hospitable for new materials. Either way, substantial changes are needed in both forks of the development pathway in order to assimilate the new opportunities offered by biomaterials in the field of tissue engineering.

COURTING CAPITAL: DEVELOPMENT OR INTEGRATION?

Jeffrey Schox, M.S., J.D.
Patent Attorney, Schox Patent Group, and Lecturer, Stanford Law School. E-mail: jeff@schox.com

There are often dozens of technologies that must be integrated to commercialize a biomaterials product and—in stark contrast with large companies—a new privately held

company ("start-up") simply does not have the resources to develop each of these technologies. A major challenge for a start-up is to determine, of the various biological, chemical, mechanical, and electrical technologies, which will be developed as new technology and which will be integrated as existing technology from other companies. Members of a start-up team typically understand that the decision to develop or integrate technologies can have an impact on product-development time and product performance; but—because of the complexities of intellectual property law—start-up scientists are often surprised by the impact of this choice on the ability of their project to attract funding from a venture capital firm.

When considering an early-stage investment in a start-up, venture capitalists evaluate both the patentability of an invention—will the start-up be issued a broad and valuable patent portfolio—and the risk of patent infringement—will the start-up infringe any fundamental patents with the commercialization of their product. Ideally, from the viewpoint of the venture capitalist the start-up has both the opportunity to own a strong patent portfolio and a clearly defined product development and commercialization pathway that avoids patent infringement.

Unfortunately, the choice between integrating or developing technologies puts these two goals into direct conflict. Integrating existing technology from another company can involve the purchase of an off-the-shelf component that includes a license to any underlying patents and potential indemnification against patent infringement lawsuits from other companies. This resolves the infringement issues but does not create the foundation for a patent portfolio. Developing and manufacturing technology can often lead to substantial improvements in product performance and reductions in costs, which can be the foundation for a strong patent portfolio but does not resolve any patent infringement issues because there can be broader patents that were filed earlier by other companies and that will prevent a start-up from commercializing its product.

In my experience, a start-up typically chooses to develop too many technologies, which increases infringement issues and reduces attractiveness to venture capital firms. Ideally, at least in its early phase, a start-up develops only its "core" technologies—the ones that differentiate the start-up from other companies and other products—and integrates other existing technologies. This strategic approach optimizes the intellectual property position of the start-up and may also minimize regulatory risk, which together strengthen the company's chances of attracting venture capital.

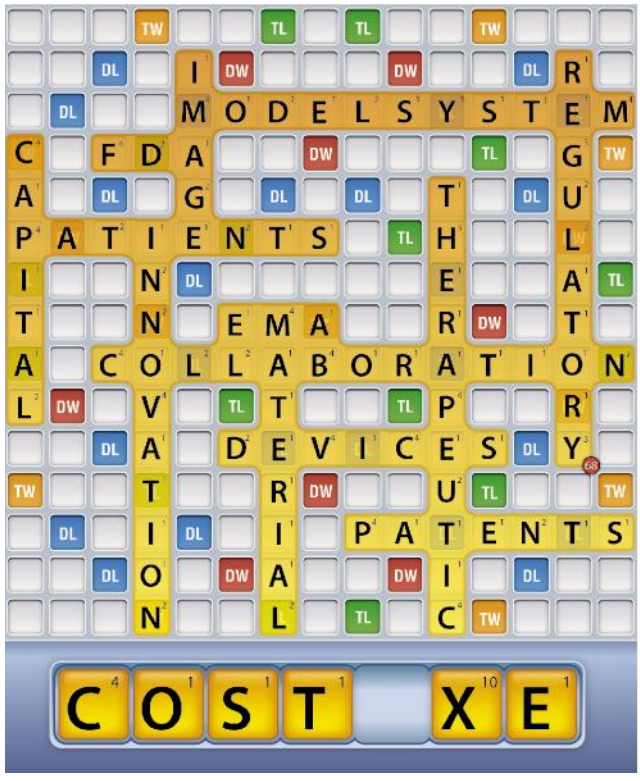
THE DILEMMA: TO INNOVATE OR TO TRANSLATE?

Sangeeta Bhatia, M.D., Ph.D.
Howard Hughes Medical Institute Investigator and Director, Laboratory for Multiscale Regenerative Technologies, Massachusetts Institute of Technology. E-mail: sbhatia@mit.edu

From my perspective in academia, there are predominantly two schools of biomaterials innovators. One pushes the boundaries of how materials interact with biological systems. These "materials innovators" design new chemistries and functionalities and largely function outside the existing translational framework. They are not encumbered by defining products and "pain points," a regulatory path, or health care costs; they are motivated purely by academic curiosity about what biology and materials can do together. These scientists are critically important to our innovation ecosystem, but their advances risk being lost in a sea of published papers.

Conversely, "translational innovators" constrain their "sandbox" to existing FDA-approved materials and GRAS (generally regarded as safe) components. They recognize that the clinical development of an invention requires definition of a product that can be sold. Traversing the clinical regulatory path is expensive, and the product must ultimately recover the investment made in its development. This cost-benefit analysis tends to block the development of material systems that might carry regulatory risk. The cost of translating new materials also can incentivize the development of expensive inventions and undermine ideas that could make health care more affordable.

Ideally, we should strive to balance the repurposing of existing materials with the invention of new ones. This compromise is important if innovation is going to drive health care, and its costs, instead of letting the regulatory framework guide and possibly restrict innovation. Such balance could be accomplished, in part, by promoting dialogue between these two worlds. Materials innovators should keep innovating even when they do not have all the answers but can be informed by the translational innovators; early visibility into how products may emerge from an invention can inform the myriad decisions that materials innovators make along the way. Translational innovators should facilitate the introduction of new material systems into humans, in spite of the increased regulatory risk, especially when the innovation enables functionality that can't be accomplished with existing materials (such as shape-memory or plasmonic materials).



Integrating innovation networks. When creative minds mesh, innovation is always possible. But in clinical translation, innovative ideas must fit within a framework that encompasses funding, intellectual property, model systems, collaboration, and regulation to ensure safety and efficacy for patients.

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Of course, there are a few centers where this convergence is already happening, and there are even some individual labs that simultaneously pursue both paths. But the conversation between innovators can and should be extended further. Several new federal translational initiatives can serve to foster this dialogue, such as the newly formed National Center for Advancing Translation Sciences (NCATS) and programs such as the proposed National Centers for Accelerated Innovation (under the National Heart, Lung, and Blood Institute). Moving forward, fostering the interaction between materials and translational researchers will create a virtuous cycle that will maximize the impact of biomaterials on human health.

NO PRECLINICAL COOKBOOK

Shannon L. M. Dahl, Ph.D.; William E. Tente, M.S.; David J. McQuillan, Ph.D.
Humacyte. E-mail: dahl@humacyte.com

When initiating a "first-in-man" clinical study for a tissue-derived biomaterial, a product safety and function data package must convince investigators, institutional review boards, and regulatory bodies that the potential benefits of the product outweigh the purported risks. Drugs and medical devices follow a refined preclinical testing framework: Animal models, study designs, statistical plans, and diagnostics practically comprise a "cookbook," which facilitates the risk/benefit analysis process for all reviewers. There is no such cookbook for biomaterials with biologic components. Thus, innovators must design their own preclinical studies, and the originality of each study design leads to a (rightfully) cautious regulatory review.

At our company, Humacyte, we are focused on producing human-derived, acellular extracellular matrices for vascular repair and replacement. These TEVGs are formed in bioreactors seeded with banked human vascular smooth muscle cells and then decellularized, yielding an acellular extracellular matrix that is stable and therefore could be readily available to patients. Our preclinical study design was shaped by factors that influence the biomaterial response in animals, including animal species, degree of phylogenetic disparity between the biomaterial and the recipient, the animal's age and growth rate, and the anatomical size of the animal and its ability to support the size of the biomaterial. As a field, our understanding of the impact of these factors on the response to a biomaterial continues to evolve. For preclinical evaluation of our TEVGs, we chose to test the actual product to be administered to humans in a nonhuman primate (NHP) model with no immunosuppression. Despite a study design that mirrored clinical application, this approach came with risks: NHPs are costly; the *n* was small compared with what reviewers expect for drug testing in smaller animals; the NHP model was new and had to be developed with surgical collaborators; and without immunosuppression, the xenogenic transplant presented a risk of rejection.

Clearly, there are many difficult considerations associated with developing a preclinical study for TEVGs and other such biomaterials. Currently, there is no publicly available guidance document from regulators to guide innovators through preclinical assessment of complex products developed with tissue-based biomaterials. In the 1980s, when recombinant protein and monoclonal antibody biotherapeutics were transitioning from bench to clinic, product development efforts benefited from "Points to Consider" documents published by the FDA that provided valuable guidance. Innovators can help by having early discussions with regulators, in which preclinical design considerations can be vetted and alignment achieved. As regulators build expectations about preclinical study designs for generalizable groups of biomaterials, regulators can help by communicating their expectations of biomaterials innovators. Public regulatory guidance not only would provide future innovators with direction on which factors to emphasize in their preclinical study designs to best support further testing in humans, it also would ease the regulatory review process because data packages for different products would look more consistent.

EVERY PATHWAY STARTS WITH A PRODUCT

Richard McFarland, Ph.D., M.D.
Associate Director for Policy, Office of Cellular, Tissue and Gene Therapies, Center for Biologics Evaluation and Research, Food and Drug Administration. E-mail: richard.mcfarland@fda.hhs.gov

National regulatory authorities have region-specific, legal definitions of medical products from which flow various regulatory pathways. In the United States, these principal definitions—drug, biologic, and medical device—may apply singly or in combination to a product. For the purposes of determining a medical product's regulatory classification, both the physical product and associated information that describes its intended clinical use (or uses) are considered. The resulting regulatory pathway is then based on how those characteristics fit the legal definitions. Biomaterials are not approved for medical uses in the United States on their own but rather as a constituent of a medical product—for example, scaffolds for cartilage repair. Because biomaterials may be incorporated in products meeting any regulatory definition (drug, biologic, device, or combination), an understanding of which pathway applies for a specific product is fundamental for prudent, expedient translation to a marketed clinical product.

Researchers must know their product sufficiently to know how their product is legally defined (which regulatory definition it meets). The FDA provides numerous ways to gather this insight, including direct interactions with the review divisions that might review a product, or the Office of Combination Products (both informally and formally). This knowledge will enable researchers to effectively develop their product in accordance with the regulatory expectation of the appropriate pathway. Failure to incorporate the appropriate manufacturing processes, controls, and testing (analytical, bench, preclinical, and clinical) into the development plan can stall translation of promising products. Although this is true for all products, the importance of incorporating knowledge of the regulatory pathway into the product development plan becomes increasingly important as products incorporate biomaterials in novel ways (or novel biomaterials, in general). Examples of such products include those in which the biomaterial or biomaterials are engineered to replicate anatomical structures (such as liver, bladder, or blood vessel), or in which biomaterials are combined with cells or other, separately regulated entities.

BIOMATERIALS AND CELLS: WELL, IT'S COMPLICATED…

Chris Mason, M.D., Ph.D.
Advanced Centre for Biochemical Engineering, University College London. E-mail: chris.mason@ucl.ac.uk

The top regulatory challenge in the clinical translation of next-generation biomaterials is undoubtedly complexity and its impact on commercialization. The long-term future of biomaterials lies in being combined with therapeutic agents, including small-molecule drugs, biologics, genes, cells, and other materials or devices to deliver cures or life-changing (transformative) therapies. These

multidisciplinary constructs are already beginning to filter through the regulatory system, thus challenging regulators to rethink their traditional methodologies, which are deeply rooted in single-platform technology products. At present, the vast majority of combination products are based on clinically approved materials, such as natural polymers, and traditional, surgically deployed biodegradable thermoplastics, including poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and polycaprolactone (PCL). A PGA/poly(lactic-*co*-glycolic acid) (PLGA) scaffold seeded with living cells has been used by Tengion to tissue-engineer replacement bladders (Neo-Urinary Conduit).

New materials that are untested in people are notably absent from tissue-engineering clinical trials. The major reason is that the route from scientific discovery to use in routine clinical practice—even for a biomaterial used on its own—has challenging technical and regulatory hurdles along the way. When materials are used in combination with another new platform technology, such as gene or cell therapy, the hurdles appear insurmountable. Indeed, after two decades, globally only a few tissue-engineered products have been approved by the regulators. Tissue-engineered combination products initially were regulated by the FDA Center for Devices and Radiological Health (CDRH). For example, tissue-engineered skin grown on a bovine collagen scaffold (Apligraf, Organogenesis) was originally approved in 1998 by CDRH. In 2012, a similarly constructed product, Gintuit (Organogenesis), was reviewed and approved by the Office of Cellular Tissue and Gene Therapies in the FDA Center for Biologics Evaluation and Research (CBER). Clearly, this FDA rationalization to have the core technologies (cells and genes) in the same FDA office as their related combination products is a win for pragmatism. Likewise in Europe, genes, cells, and tissue-engineered medical products are all covered by the Advanced Therapy Medicinal Products (ATMP) regulation.

Long development timelines, funding shortages, and regulatory uncertainty hinder the clinical translation and commercialization process for combination biomaterials. The majority of companies working in this space are small start-ups. Venture capital funding is hard to get and is of limited duration (typically 5 to 7 years). Any hiccup in the process that creates a slight stall in a product's progress can mean the downfall of a company, especially single-product ones. Thus, investors and investigators alike focus on removing complexity, by going with either cells or the biomaterial alone, to ease the regulatory burden and reduce uncertainty. Unfortunately, this strategy is in opposition with the diverse range of unmet clinical needs (many of which will not be solved by one technology alone) and the ability of the field to achieve its full potential through the development of multifunctional combination materials. The regulatory moat—which is at present too wide and too deep for all but the big multinationals—must be bridged. One hopes that the FDA Safety and Innovation Act (signed into law on 9 July 2012), which includes the reauthorization of the Prescription Drug User Fee Act, will evolve into an exemplar to accelerate the regulatory approval of the tsunami of game-changing combination biomaterial products looming on the scientific horizon.

ACCEPTING THE POSSIBILITY OF FAILURE

Jonathan Sackner-Bernstein, M.D.
Vice President, Clinical Development and Regulatory Affairs, NeoStem. E-mail: jsb@neostem.com

In 1901, President McKinley initially survived an assassination attempt. Rushed to the operating room, his surgeons raced to save his life. Working via reflected sunlight and candles, the surgeons felt around in his abdomen for the bullet, eventually deciding to leave it inside him when they could not feel it. As the operation was concluding, so the story is told, a rudimentary electric light was brought into the operating theater but was not used. In the days after the operation, Thomas Edison delivered an early-generation x-ray machine to help the doctors locate the bullet. Once again, the potential benefits were not recognized and this advanced tool sat idle. Several days later, McKinley died with the bullet still lodged in his abdomen.

In the past century, technologies such as magnetic resonance imaging, angioplasty, and artificial joints overcame the technical, clinical, financial, and regulatory barriers to transform lives. These successes are few compared with the number of promising medical products squelched during development, many by regulatory requirements and regulatory uncertainty. Convention tends to be favored rather than considering the potential for transformative impact of unfamiliar tools. As technology, including biomaterials, becomes more complex, regulators face the challenge of balancing between the potential benefits of innovation (new materials) and the lack of additional risk to the public from using only what is already approved. To resolve this conundrum, should a regulator adopt the "zero risk tolerance" reinforced by Congress, the media, and the public? This extreme prevents development of new biomaterials and medical products, although few would advocate that regulators should allow untested products to be marketed.

When metal-on-metal hips were proposed for clinical use, experts suggested that this material would benefit patients by providing a more durable implant. Scientific and clinical knowledge was applied rigorously but was flawed because we did not yet know that in a small proportion of patients, metal debris from these materials could cause soft tissue necrosis. Such unanticipated failure can happen with new biomaterials, new uses of existing biomaterials, and medical products in general. To reduce human suffering and address rising health care costs, society and Congress first must be willing to accept the possibility of failures en route to progress and champion this perspective while regulators adopt it. Only then will the product developers have the opportunity to create disruptive innovations that recalibrate quality and cost of care.

To reconfigure the medical product development landscape to accept the possibility of failure, we will need to define an acceptable frequency and severity of these failures. Although it seems unrealistic to advocate for lax standards for use of innovative products, it is perhaps rational to adjust the requirements to start clinical trials earlier. For example, instead of requiring a wide range of animal tests that may not predict human safety or efficacy, why not skip the time- and cost-intensive studies and launch clinical trials for patients with no other options? This will not identify rare events, as exemplified by the metal-on-metal hip example, but may provide opportunities sought by desperate patients and innovative product developers. If imagined risk trumps potential benefit, and barriers to translation seem insurmountable, our society also faces the possibility of losing innovators to opportunities outside of the United States as well as to unrelated fields of science.

SYNTHESIS: STAY FOCUSED ON THE CLINICAL NEED

Glenn D. Prestwich, Ph.D.
Presidential Professor of Medicinal Chemistry and Presidential Special Assistant for Faculty Entrepreneurism, Center for Therapeutic Biomaterials, University of Utah. E-mail: gprestwich@pharm.utah.edu

The known unknown. When riding the translational roller coaster, academic, industry, and regulatory scientists must stay focused on the clinical problem.

Eight experts with insider insights each described different challenging aspects of the development and approval of clinical biomaterials. Together, these opinions emphasize that biomaterial translation is neither a linear nor a well-scripted process that progresses predictably from an idea to an approved product. At this stage, the many "known unknowns" make it more like a disorienting roller coaster ride; but on this ride, it is crucial to stay focused on the clinical problem. To reach the end of the ride intact, innovators must negotiate twists and turns associated with seven "wheels": (i) intellectual property, (ii) preclinical development, (iii) multiple regulatory pathways, (iv) business strategy and financing, (v) product development, (vi) clinical trial designs, and (vii) reimbursement. All travel together; if one wheel is lost, the project can derail.

As our insiders note, a team approach is essential and requires frequent communication and mutual trust among all stakeholders—academic, regulatory, corporate professionals, and end-users. Constant, critical reevaluation of the key parameters is crucial. Translation of biomaterials to the clinic takes strong intellectual property, a business model that makes sense to investors, and a product that physicians will prescribe and that benefits patients.

To succeed in translation, one must balance innovation and practicality. But underlying this risk-benefit analysis are several immutable principles. First, the product must be safe. This is the most important preclinical requirement in both the European Union and the United States to initiate clinical studies. Second, the product should be effective in treating the clinical need. Third, from a strategic research and development point of view, the product should work in patients as expected from preclinical data. The obvious question for a drug is, "Does it hit the target?" For a clinical biomaterial, the question is less clear. Last, from a business development and financing viewpoint the ultimate question is, "Will users adopt this product?" A great product that does not gain traction with physicians and patients, generate revenue for the company, or qualify for reimbursement will ultimately fail.

The translational imperative for innovators of a clinically useful biomaterial is threefold: (i) embrace complexity, (ii) engineer versatility, and (iii) deliver simplicity. Rather than engineering a complex solution to a clinical need, the preferred starting business model would be to allow biology to do the heavy lifting. This approach involves deconstructing biological complexity to simpler components. A single formulation cannot fulfill every need, from rebuilding ischemic brain or heart tissue to repairing a scarred vocal fold. Thus, the engineering of compositional and mechanical flexibility into a biomaterial accesses a portfolio of products based on a few approvable components. Last, to reach the clinic, all stakeholders in translation demand simplicity. Acceptance of a new technology is not determined solely by improvement in patient outcome; often, the true limiting factors are cost, familiarity, ease of use, and reimbursement.

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