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Enhancing Tissue Engineering and Regenerative Medicine Product Commercialization: The Role of Science in Regulatory Decision-Making for the TE/RM Product Development

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TERMIS-AM Industry Committee (TERMIS–AM/IC), in collaboration with the TERMIS-Europe (EU)/IC, conducted a symposium involving the European Medicines Agency and the U.S. Food and Drug Administration (FDA) toward building an understanding of the rational basis for regulatory decision-making and providing a framework for decisions made during the evaluation of safety and efficacy of TE/RM technologies. This symposium was held in August 2012 during the TERMIS-WC in Vienna, Austria. Emerging from this international initiative by the European Union and the United States, representatives from the respective agencies demonstrated that there are ongoing interagency efforts for developing common national practices toward harmonization of regulatory requirements for the TE/RM products. To extend a broad-based understanding of the role of science in regulatory decision-making, TERMIS-AM/IC, in cooperation with the FDA, organized a symposium at the 2014 TERMIS-AM Annual Meeting, which was held in Washington, DC. This event provided insights from leaders in the FDA and TERMIS on the current status of regulatory approaches for the approved TE/RM products, the use of science in making regulatory decisions, and TE/RM technologies that are in the development pipeline to address unmet medical needs. A far-ranging discussion with FDA representatives, industrialists, physicians, regenerative medicine biologists, and tissue engineers considered the gaps in today's scientific and regulatory understanding of TE/RM technologies. The identified gaps represent significant opportunities to advance TE/RM technologies toward commercialization.

Introduction

In 2010, the TERMIS-Americas Industry Committee (TERMIS-AM/IC) began to delineate potential opportunities to enhance commercialization of products highlighted by the TERMIS constituency.[1] Significant opportunities for enhancing the commercialization of tissue engineering and regenerative medicine (TE/RM) technologies were identified. Included among these were access to capital for advancing potential technologies into development and promoting the understanding of regulatory decisions.[2–5] Highlighted by the TERMIS constituency was a need for broadening their understanding of regulatory decisions and how science is used in the regulatory decision-making process.[6]

In 2013–2014, TERMIS-Americas (AM) members were surveyed by the Industry Committee to evaluate their awareness of regulatory requirements for the tissue engineering and regenerative medicine (TE/RM) product development.[6] The survey revealed that 80% of the TERMIS-AM membership taking the survey claimed involvement in the development of TE/RM products. While this was the case, awareness of the Food and Drug Administration (FDA)

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Table 1. Commercial Cell Therapy Product Including Leading Products[10]

Skin	**Dermagraft**
	Apligraf
	Epicel
	ReCell
	BioDFactor
	GINTUIT
	Grafix
	Epidex
	EpiGraft
Skin—aesthetic	LaViv
Bone	**Osteocel**
	AlloStem
	Trinity/Trinity Evolution
	PureGen
Heart	Heartcellgram-AMI
Cartilage	**MACI**
	Carticel
	ChondroCelect
	BioSeed-C
	DeNovoNT
	Co.don Chondrospheres
	Cupistem
	Cartistem
Antiadhesion	BioDence
Antiscarring	Nucel
Cancer treatment	Provenge
Eye	Prokera
	AminoGraft

Leading products are highlighted in bold.

regulations varied markedly across academic, industry, and government members and did not correlate with the active development of a TE/RM technology. Notably, members from for-profit companies, consultants, and the government performed best in the survey, whereas students, professors, and respondents from outside the United States performed less well. Interestingly, a subset in all groups, including students, demonstrated a broad knowledge of FDA regulations. A few members highlighted their need to expand the understanding of regulations involved in commercialization of TE/RM products and are participating in standards organizations or regulatory educational programs to strengthen their knowledge of FDA regulations for the development of TE/RM products. The survey concluded that very early exposure to regulatory experts is likely to be of value for those seeking to ultimately bring their technology to the market. The authors went on to suggest that a formal education in regulatory science may enhance translation of tissue engineering research and development. Furthermore, opportunities for the TERMIS membership in advancing their technologies toward commercialization included involvement in standards development organizations and formal regulatory science exposure, concurrent with the scientific activities involved in the development of their technology.

Highlights from a Review of Scientific Principles in Regulatory Decision-Making

A series of presentations highlighted the role of science in the development process for the TE/RM products. Discussing the changing global environment of the TE/RM technologies was Dr. Chris Mason, Professor, University College London. He highlighted the opportunities for regulatory innovation in cell-based therapies as this new technology represents a ''4th'' pillar in healthcare products together with pharmaceuticals, medical devices, and novel biotechnologies. With over 20 approved cell-based therapeutic products generating combined revenues of over $1B/year in sales (Table 1), more than 300 cell-based therapy companies around the world could bring significant advances to unmet medical needs.[7] With changes in healthcare outcomes linked to personalized medicine and the potential for point of care delivery, new innovations in infrastructure, including regulatory guidelines, are needed to bring innovative therapies to underserved patient populations.

Dr. Mason highlighted that with the advent of more cell-based therapies regulated as combination products, there is a need for modernization of regulatory science to review complex mechanisms whereby regenerative products are providing improved outcomes. In addition, complex manufacturing processes require regulatory updates on how products are manufactured and delivered to the patients. He also highlighted that professional education of physicians must focus on professional training to accommodate emerging product advances. The regulatory dilemma for such advances is realized by the balance of the following: (i) being overly tolerant of new medicines that, once on the market, are shown to be unsafe and (ii) while a ''too risk averse'' approach leading to increases in opportunity costs, stifling innovation, ultimately leaving patients with unmet medical needs wanting for improved healthcare outcomes.[8] Clearly, regulators are considering these innovations by establishing the Advanced Therapy Medicinal Products pathway in the European Union, conducting parallel reviews by the FDA and Center for Medicare and Medicaid Services (CMS), and the initiative of Japan's Ministry of Health, Labor, and Welfare, which considers novel legal and regulatory frameworks for cell-based therapy by offering conditional term-limited authorization earlier in the development pathway.

Representing the FDA were leaders from the respective centers that regulate TE/RM products (i.e., Center for Biologics Evaluation and Review [CBER] and Center for Devices and Regulatory Health [CDRH]) as well as a chief sciences officer. These included the following: Carolyn Wilson, PhD, Associate Director for Research, CBER, FDA; Steven Bauer, PhD, Chief, Cellular and Tissue Therapy Branch, CBER, FDA; and James Coburn, MS, CDRH, FDA. They highlighted that the FDA's principles of safety and efficacy/effectiveness apply to all TE/RM technologies. Importantly, products developed by TE/RM technologies, like other medical products, are subject to the Code of Federal Regulations 21 (CFR 21) as the basis for how the FDA regulatory guidelines are applied to product development, manufacturing, and commercialization. All participants and panelists recognized that the challenges for regulating TE/RM products result from gaps in the science and the absence of scientific, clinical, and regulatory precedents, few/no regulatory guidelines, and jurisdictional overlaps. However, the FDA's broad experience and subsequent policy development with different novel technologies are based on a robust regulatory scientific understanding capable of evaluating the complexities of the TE/RM products.

Established risk-based approaches for all medical products consider patient risk, product understanding, and clinical

indication to evaluate the expected health benefit/value. The FDA reviews each regulatory submission on its own merits and maintains active intramural and collaborative regulatory science research programs through CBER, CDRH, and Centers of Excellence in Regulatory Science and Innovation (CERSI). To ensure that FDA reviewers are up-to-date on the latest scientific advances, the FDA has established broad-ranging intramural and extramural programs for the TE/RM products.[9] FDA's Regulatory Science programs provide proactive approaches for ensuring public health with complex TE/RM products.

With TE/RM products, rational decisions and subsequent policy development for TE/RM products are driven by the science, data, and internal and external experts. Multiple centers provide input for evaluation of TE/RM combination products. This effort encompasses research in novel product areas by scientific staff and reviewer training in novel science in support of TE/RM review and regulation. The FDA uses developing TE/RM products as case studies for evaluating the safety and efficacy/effectiveness of new products.

An illustration of FDA's leadership role in elucidating the scientific basis of novel technologies is FDA's Mesenchymal Stem Cell Consortium, which is focused on evaluation of MSC heterogeneity and potency to improve the characterization of cellular products for clinical development. Results indicate that cell potency assessment requires assays of cellular differentiation potential since cell markers do not correlate with heterogeneity, donor selection, or culture method. Cell identity and potency assays are foundational in predicting safety and efficacy by demonstrating the relationships between cellular characteristics and clinical response. The FDA principles of testing and quality control are integral for TE/RM products to ensure the safety and efficacy/effectiveness for each approved product.

New product considerations also include known safety concerns regarding material composition, cellular composition, and interactions between components, as well as biocompatibility, mechanical properties, surface characteristics (e.g., nanotechnology), design limits, sterilization/storage, possibly, additional information on new or existing safety concerns.

Established manufacturing processes and standards guide FDA's approach to new methods, as highlighted by advances in Additive versus Subtractive manufacturing. Quality control for manufacturing is dependent on process, material process, and quality systems.

Key Learnings from a Panel Discussion on the Application and Limitations of Science in Regulatory Decision-Making

A panel composed of regulatory, clinical, and industrial experts, knowledgeable in TE/RM product development, discussed the application and limitations of scientific understanding in regulatory decision-making. Representing the FDA was Celia Witten, MD, PhD, Director, Office of Cellular, Tissue and Gene Therapies, FDA. Representing academia and the role of physicians in the development of TE/RM products was Trinity Bivalacqua, MD, PhD, Associate Professor, Johns Hopkins University. Two industrial leaders were Marc Hedrick, MD, President and CEO, Cytori and Geoff MacKay, formerly President and CEO, Organogenesis, Inc.

The panel discussed several challenges for TE/RM product development relating to the state of current scientific understanding. Although unique in many ways, TE/RM products are a diverse collection of products that have similar translational challenges as other medical products. Notable was the fact that the clinical standards of care have not been established for TE/RM clinical trials, thus making the translation of animal to human outcomes challenging. The panel agreed that there is a need for scientific analysis and clinical rigor to align with regulatory expectations and that, more understanding is needed of translational medicine approaches for TE/RM products, including how they will be used in clinical practice.

A significant complicating aspect of clinical trials is linked to the heterogeneous patient population and underlying pathophysiology overlay in the exploratory trial phase (no healthy volunteer phase) for the TE/RM product development. There is a need for more clarification of the definition of clinical success and endpoints that characterize new/improved functional organ/tissues. This was highlighted by a recognition that clinical endpoints acceptable for regulatory approval must align with agreed clinical endpoints and medical communication.

Unique trial designs may be important for trial conduct (e.g., iterative vs. parallel recruitment), and modifications may be needed of the current standard clinical trial conduct for the TE/RM products. Additional challenges exist to define appropriate preclinical models applicable for clinical translation—for example, clinical trial design, endpoint, and biology of TE/RM product's therapeutic action. Also relevant are gene and biochemical pathway interactions that impact the complex process of regeneration versus single gene/enzyme effects of a molecular drug entity.

TERM product development may have unique challenges, which involve the science, technology, and clinical trial design and conduct, and may have different outcomes from that of a drug or device. However, with more industrial focus on developing the TE/RM products, scientific and regulatory guidelines/standards will be developing rapidly. The importance of an interdisciplinary effort for evaluating the potential mechanisms to address the challenges in clinical translation and partnerships with professional clinical organizations and TERMIS/regenerative medicine scientific organizations may advance this effort to accelerate TE/RM product development in the clinical stages. Also, highlighted was the need for clinician training with the current state of TE/RM of technology.

Advancing Regulatory Science Through Expanded Education

A series of presentations were made on the need for educational enhancement to understand the role of science in regulatory decision-making for those involved in the TE/RM product development.

Peter Johnson provided an overview of the AM IC Survey.[6] Representing the FDA were Leslie Wheelcock, MS, RN, Director, Office of Scientific and Professional Development, FDA and Carmen Gacchina Johnson, PhD, FDA Commissioner's Fellowship Program. Esin Yesilalan, MSc, Senior Regulatory Scientist, Voisin Consulting, Inc. provided insights as an individual with initial academic and

subsequent industry experiences and now serves as a regulatory consultant for Voisin Consulting, Inc.

The FDA presenters highlighted that the FDA is pursuing numerous activities to address the regulatory knowledge gap to aid TE/RM product development. One important mechanism for an individual is submitting a product for FDA review to utilize the presubmission feedback or ''Q'' meeting approach, so that sponsors and FDA can align on the most critical activities of a sponsor's development plan. FDA's initiatives are targeted to help translational science shape basic scientific discoveries into treatments by strengthening the clinical trial enterprise.

The FDA also has multiple activities for others working in the area of TE/RM, including online education for students, academia, and industry on FDA website; speakers at conferences such as the TERMIS-AM 2014 Annual Meeting; and Academic Programs with Centers of Excellence in Regulatory Science. In addition, FDA has formed alliances with academic centers including, but not limited to, the University of Maryland, Georgetown University, University of Arkansas, Stanford University, and Johns Hopkins University. The FDA also has training programs in collaboration with the Institute of Medicine and an internal program for students to learn about the FDA (i.e., Commissioner's Fellowship Program).

Student scientists can look to progress from an academic exercise to a development/commercial focus through multiple pathways. Networking, mentoring, and engaging in product development activities and self-teaching activities enable this transition. The FDA has a broad array of activities that includes support of Translational Medicine Initiatives, Regulatory Paradigms for evaluating Clinical Translation, emerging regulatory guidelines for TE/RM products, and working among international regulatory agencies to collaborate on specific regulation(s) for the TE/RM products.

Importantly, the FDA is focused on ensuring that the review process of TE/RM products is conducted with the highest scientific rigor. The FDA makes every effort to train their staff, support sponsors, and work toward ensuring that the public's health is maintained with the most advanced medical products available to address unmet medical needs and aid underserved patient populations. Ultimately, the FDA evaluates TE/RM with the same scientific paradigms used for other products and recognizes that the TE/RM technologies may be unique, but the principles of regulatory evaluation are not.

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