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## *Prospects for Harmonizing Regulatory Science (RS) Programs in Europe, Japan, and the United States to Advance Regenerative Medicine (RM)*

Christopher-Paul Milne, James Mittra, Naoko Kojima, Daisuke Sugiyama, Josephine Awatin, and Gabrielle Simmons

### **INTRODUCTION**

Though great progress has been made in medicine, current evidence-based and palliative treatments are unable to keep pace with patients' needs, especially given aging populations. There are few effective ways to treat the root causes of many diseases, injuries and congenital conditions. In many cases, clinicians can only manage patients' symptoms using conventional therapy. Regenerative medicine (RM) is a game-changing area of medicine with the potential to repair damaged tissues and organs, and bring hope to patients with debilitating illness. The body's ability to rebuild itself at many different levels using complex mechanisms means RM promises to be a valuable tool in most medical specialties<sup>1</sup>

RM itself is not new, and its underlying technologies are based on over 50 years of research in stem cell biology, molecular biology, engineering, advanced materials, immunology and genomics. Its growing importance was recently highlighted by a government report to the US Congress showing that 22 of 27 institutes within the National Institutes of Health (NIH) funded RM research projects from 2012 through 2014, and that for six of these institutes RM awards comprised 7% or more of research funding, including a quarter of the total funding awards from the National Heart, Lung, and Blood Institute.<sup>2</sup> The field has taken a major leap with the clinical introduction of cell and gene-based therapies, which can cure underlying disease, rather than simply manage symptoms or slow disease progression.<sup>3</sup> With its power to restore and regenerate regardless of the underlying medical indication (e.g. aging, cancer, trauma), RM is poised to transform the therapeutic landscape in much the same way as antibiotics and biotechnology did in previous decades. Antibiotics transformed the treatment of bacterial infections in the 1940s, and in the process enabled the emergence of the big pharma industry. Recombinant proteins and monoclonal antibodies produced the next industry step change, and launched the biotechnology sector. RM technologies, like cell and gene therapies, are the most recent major advancement in healthcare, and represent a significant commercial opportunity.<sup>4</sup>

There are many challenges facing the successful introduction of RM into the clinic, and these apply to a greater or lesser extent in all the major regions of the world where medical innovation is taking place. These challenges include limited funding due to uncertain commercial pathways,<sup>5</sup> challenges facing reimbursement and clinical uptake for therapies that are very different from conventional drugs,<sup>6</sup> and significant manufacturing and scale-up challenges at various stages of clinical development.<sup>7</sup> All of these challenges are compounded by regulatory and policy systems designed for conventional small-molecule drugs, which are struggling to adapt to the emergence of radically new therapeutic paradigms.<sup>8</sup>

The regulatory agencies of the three major drug-development regions in the world – Europe, Japan & the US – are struggling to make appropriate regulatory decisions about advanced technologies that are highly promising, but also uncertain and potentially risky – the

so-called regulatory paradox.<sup>9</sup> Is regulatory science (RS), applying science-based approaches and standards to support regulatory decision-making, the right set of tools for calibrating a uniform set of regulatory mechanisms needed to integrate RM into the mainstream of the development continuum for medical products? We will examine the current state-of-the-art for RM and RS in the 3 major drug development regions to answer this question.

## WHAT IS REGENERATIVE MEDICINE?

At a conceptual level, RM can be defined by three interrelated approaches:

- *Rejuvenation*, which means boosting the body's natural ability to heal itself. Cells in the body once thought to be no longer able to divide (terminally differentiated) — including the highly specialized cells constituting the heart, lungs and nerves — have been shown to be able to remodel and possess some ability to self-heal.
- *Replacement* involves using healthy cells, tissues or organs from a living or deceased donor to replace damaged ones, and expanding opportunities for organ transplants by finding ways to overcome the ongoing donor shortage, the need for immunosuppression and challenges with organ rejection.
- *Regeneration* involves delivering specific types of cells or cell products to diseased tissues or organs, where they will restore tissue and organ function. This can be done through cell-based therapy or by using cell products, such as growth factors, or bone marrow transplants.<sup>10</sup>

At a practical level, RM can be defined as products incorporating viable cellular components intended to repair, replace or restore diseased, damaged or missing tissues (i.e., 'healing from within'),<sup>11</sup> which can be broken down into the following categories (see Table I):<sup>12</sup>

*Cell Therapy* – is the use of living cells as therapies, ranging from established techniques such as bone marrow transplantation to more novel approaches using stem cell biology.<sup>13</sup> Stem cells have the ability to develop — through a process called differentiation — into many different types of cells, and offers new clinical applications to treat or manage chronic diseases such as diabetes, heart failure, and degenerative nerve, bone and joint conditions. RM researchers are investigating both adult and embryonic stem cells, as well as various types of progenitor cells, such as those found in umbilical cord blood, and bioengineered cells called induced pluripotent stem cells (iPS). The latter are adult cells that have been genetically re-programmed to an embryonic cell-like state, and are particularly useful for studying neurodegenerative diseases like Alzheimer's, because, among other advantages, they allow scientists to study the very early stages of the disorder.<sup>14</sup>

*Gene therapy* – is the therapeutic manipulation of individual genes or cell populations for the treatment of a disease. For example, several inherited immune deficiencies have been treated successfully with gene therapy. In the most common technique, blood stem cells are removed from patients, and retroviruses are used to deliver working copies of the defective genes before the cells are returned to the patient. Because the cells are treated outside the patient's body, the virus will infect and transfer the gene to only the desired target cells. Others are looking to expand this approach to mainstream diseases with gene therapy involving the delivery of beneficial genes to over-express their products at a site of damage in the body; for example,

using the common cold virus to deliver the gene that grows new blood vessels (VEGF) to the heart in patients with angina.<sup>15</sup>

*Tissue engineering* – is using advanced materials and nanomaterials combined with cells to produce functional tissues and organs by means of combining cells, biologically active molecules, and scaffolds that support the tissue growth until it generates functional tissue (the field also includes bio-aesthetic medicines, i.e., medical therapies that generate new and aesthetically appealing tissues).

**TABLE I**

<b>Therapy</b>	<b>Indication</b>	<b>Product</b>	<b>Manufacturer</b>
Cell Therapy	Advanced leukemias	T cell-based immunotherapies for acute lymphoblastic and chronic lymphocytic leukemias	UPenn/Novartis; Juno Therapeutics
	Cartilage regeneration in the knee	Carticel, ChondroCelet	Aastrom Biopharmaceuticals (now Vericel Corp.); TiGenix
	Cardiac disease - Chronic heart failure	Adult stem cells	Mesoblast/Teva Pharmaceuticals
Gene Therapy	Hemophilia	Factor 9 deficiency	St. Jude's/University College London; Spark Therapeutics; Baxter International Inc.
	Inherited metabolic disease - familial lipoprotein lipase deficiency	Glybera	UniQure
	Inherited immunology disorders	Severe combined immune-deficiency (SCID)	GlaxoSmithKline/Molmed
Tissue Engineering	Chronic venous leg ulcers– Tissue-engineered skin replacement	Apligraf, Dermagraft	Organogenesis
	Diabetic foot ulcers - Tissue-engineered skin replacement	Apligraf	Organogenesis
	Corneal blindness – Adult stem cell-based therapy	Holoclar	Chiesi
	Severe burns – Tissue-engineered skin	Epicel	Aastrom Biopharmaceuticals
	Gum regeneration – tissue-engineered soft tissue to restore healthy gums	GINTUIT	Organogenesis

## **ROLE OF REGULATORY SCIENCE IN REGENERATIVE MEDICINE**

The regulatory agencies of the three major markets all use the term regulatory science, but have assigned different priorities for its implementation and employ different methods for utilizing it, particularly with regard to RM. In other words, they define it similarly, but apply it differentially.

### **Europe**

Regulatory science is defined by the European Medicines Agency (EMA) as the range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine especially in areas of emerging and innovative sciences. It encompasses basic and applied medicinal science and social science, and contributes to the development of regulatory standards and tools.<sup>16, 17</sup> The primary impetus for its emergence was its applicability to advanced technologies in Europe through the adoption in 2007 of Regulation (EC) 1394/2007 on Advanced Therapy Medicinal Products (ATMP Regulation), which specifically enumerated 3 types of ATMPs: gene therapy; somatic cell therapy; and tissue engineered products.<sup>18</sup> The European ATMP regulation forms part of the centralized procedure for the approval of new, advanced medicines to create a viable pathway to market for therapies that could not easily be evaluated and given a market authorisation through conventional regulatory processes. It includes four key measures. First, the ATMP created a central marketing authorisation procedure for all advanced therapies, including both autologous (i.e., patient is the donor) and allogeneic (another person is the donor) cell therapies and tissue-engineered products.<sup>19</sup> RM based on extensively manipulated cells, or those modified on an engineered process, are subject to the regulation. Unmodified cells used in transplants do not fall within the regulatory framework, so the regulation does not try to capture technologies and techniques that have been used routinely for decades. Second, the ATMP included the establishment of a Committee for Advanced Therapies (CAT) within the EMA to provide technical advice and establish guidelines for good regulatory science. Third, the regulation established special incentives to support innovation in small and medium-sized companies, which are driving most of the path breaking science and technology underpinning RM. Fourth, the ATMP made a distinction between ‘hospital-based’ and ‘commercial research,’ by allowing for what is controversially known as the ‘hospital exemption’ (HE) for autologous treatments.<sup>20</sup> The HE was to allow experimental treatments to be developed and delivered within hospitals for patient benefit, without medical practitioners having to apply for a full market authorization and meet strict regulatory requirements. However, these products were still expected to meet safety and quality standards set by national regulatory bodies.

### **Japan**

In Japan, regulatory science refers to the science of predicting, evaluating, and determining, fairly and promptly, the quality, efficacy, and safety of pharmaceuticals, medical devices, and RM products, based on scientific knowledge.<sup>21</sup> In April 2009, the Pharmaceuticals and Medical Devices Agency (PMDA) established an Office of Regulatory Science (ORS) and a Regulatory Science Research Division in ORS. In 2011, they established the Office of Standards and Guidelines Development, a dual structure office with the Division of Standards for Drugs

and the Division of Standards for Medical Devices, through which they are developing standards and guidelines by systematizing the review information as well as the outcomes of research on regulatory science. In 2012, PMDA established a Science Board of external experts to pursue regulatory science, enhance cooperation and communication with academia and medical institutions, and keep pace with the advancing science and technology utilized in the products.<sup>22</sup>

At a practical level, the primary application of regulatory science in Japan has been to facilitate development and review of RM. Japan has one of the highest proportions of aged individuals globally, and cell and tissue based products were beginning to show promise for addressing the consequent health problems, however, regulatory oversight in the new field of RM was outdated and inadequate. For these reasons, in April of 2013, Japan passed the Regenerative Medicine Promotion Act to establish the government's responsibility to regulate RM.<sup>23</sup> This stage-setting legislation was soon followed by the "The Act on the Safety of RM" and the "Pharmaceuticals, Medical Devices and Other Therapeutic Products Act" (PMD Act), which created the current regulatory framework. The former law promotes RM by facilitating clinical studies, while ensuring safety with oversight of in-house clinical research and medical practice, as well as assuring quality with standards in good tissue practice (GTP), while allowing outsourcing of cell culturing and processing.<sup>24</sup> The latter permits a product sponsor to get conditional marketing approval based on results from mid-stage, or Phase II, human trials that demonstrate safety and probable efficacy. Conditional approval means that the firm will be able to sell its treatment while continuing to gather data on efficacy for a period of up to seven years. At the end of the seven year period, the firm must either apply for final marketing approval or withdraw the product.<sup>25</sup> Proponents of the regulatory upgrade believe that now there is an approximately three-year trajectory for approvals compared with seven to 10 years before the laws' implementation.<sup>26</sup>

## **United States**

Regulatory Science, as defined by FDA, is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products. On February 24, 2010, FDA launched its Advancing Regulatory Science Initiative, building on the achievements of existing programs, like Critical Path. Its implementation is overseen by the Office of Regulatory Science and Innovation. According to FDA, stem cells, engineered tissues, and combination products are areas of rapidly emerging technology for which intervention will be necessary to bridge the gap between innovation and the market. FDA recognizes the importance of RM and has made an effort to interact with the development community and NIH to consider standards and models in this area.<sup>27</sup> Indeed, FDA's global engagement strategy proposes a strong reliance on regulatory science to ensure that FDA is engaging with global partners to harness scientific developments and pool products, resources, and expertise to support science-based regulatory decision-making and pursue the best public health solutions.<sup>28</sup>

On the one hand, FDA scientists appear to use most of the FDA's allotted RM funds (about \$8.63 million) to advance regulatory science, such as improving methods for evaluating experimental cell-based products to reliably predict product performance. On the other hand, Table II <sup>29</sup> illustrates how FDA's Regulatory Science strategy is viewed by some observers as applying to RM/Stem Cell Science only in broad strokes.

**TABLE II**

<i>Regulatory science strategic area</i>	<i>Examples of relevance for stem cell–based regenerative medicine</i>
1. Modernize Toxicology to Enhance Product Safety	NIH NCATS grant: Human induced pluripotent stem cell and embryonic stem cell-based models for predictive neural toxicity and teratogenicity
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes	NIH NCATS grant: Modeling complex disease using induced pluripotent stem cell-derived skin constructs
3. Support New Approaches to Improve Product Manufacturing and Quality	Quality by Design in Stem Cell Transplantation
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies	Participation in public hearings of the FDA advisory committees on market authorization applications in respect of stem cell–based regenerative medicines
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes	Application of the technology embodied in the Stem Cell Matrix, an innovative information system
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health	The use of stem cell lines for food safety tests

7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security	U.S. Biomedical Advanced Research & Development Authority (BARDA): Mesenchymal Stem Cells to Mitigate and Treat Cutaneous Injury Following Radiation; Irradiated Hosts on Transplanted Hematopoietic Stem Cells
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Product	References to FDA's efforts at community outreach in November 2012 report on the elements of regulatory science applicable to RM&SC by the Office of Cellular, Tissue and Gene Therapies in FDA's Center for Biologics Evaluation and Research.

## CURRENT STATE-OF –THE –INDUSTRY FOR REGENERATIVE MEDICINE

### Market Value Estimates

Predictions for global market for RM products in 2020 range from as low as \$11 billion,<sup>30</sup> to as high as \$ 67.6 billion, at a cumulative annual growth rate (CAGR) of 23.2% during the years 2014 and 2020.<sup>31</sup> According to a recent market research report, North America and Europe accounted for over 75% of the market revenue in 2013 and is projected to be the most lucrative regional market. However, there is believed to be an increase in technological adoption and emphasis on RM research in Japan and South Korea, with the Asia-Pacific region as a whole considered to be the fastest growing region for the RM market.<sup>32</sup> Japan's market alone is poised to grow from 9 billion yen in 2012 to 1 trillion yen in 2030.<sup>33</sup> It is no surprise that many analysts feel the sector is entering a significant inflection phase,<sup>34</sup> because of a convergence of key market factors including: an ever-aging population, increasing patient expectations, diminishing Big Pharma pipelines, and significant corporate investment by the majority of the Big Pharma companies.<sup>35</sup>

Unmet medical needs that could be addressed by RM therapies provide additional support for this assessment. In Europe, for example, primary immune deficiencies (PIDs) are a growing group of over 230 different disorders exemplified by the condition, ADA-SCID, also known by its media moniker as the "bubble boy disease." By itself ADA-SCID is commercially a very small market, however, the field has potential to widen into the mass-market condition of heart failure.<sup>36</sup> In Japan, there are over 4.6 million people living with Alzheimer's Disease, and by 2050, the socio-economic cost will be greater than the Japanese government's annual income unless effective treatment becomes available.<sup>37</sup> In the US, there are 132 million MD office visits, 29 million ER visits, and 15 million out-patient visits for musculoskeletal-related conditions per year with estimated annual direct and indirect healthcare costs of \$850 billion.<sup>38</sup>

### R&D Funding



Overall, the RM investment horizon has brightened considerably according to highlights from the Investors Day meeting held by the Alliance for Regenerative Medicine (ARM) in late March of 2015: venture capital investments nearly doubled; funding from initial public offerings (IPOs) were close to tripling; and, up-front partnership payments rose almost 8-fold.<sup>39</sup>

In Europe, a recent spate of deals has ignited investor interest in gene therapy and several large drug-makers are now buying into a high-risk field that is recovering from some disastrous clinical trial results in the late 1990s and early 2000s. In 2014, gene therapy attracted \$3.0 billion in financing, up 510% on 2013, and the pace has continued in 2015.<sup>40</sup> The European Commission's Horizon 2020 funding call, together with the Innovative Medicines Initiative, will provide over 10 billion euros in research funding opportunities over the next 5 years, making the EU more attractive than ever for gene and cell therapy sector possibilities to create innovative consortia in collaboration with industry, bring novel products to market, and build sustainable networks of expertise in the field.<sup>41</sup>

In Japan, the Forum for Innovative Regenerative Medicine (FIRM) was incorporated in 2011 to pursue broad, industry-led partnerships with governments, universities, and the private sector for the purpose of building a great consensus on the commercialization process. It currently consists of 185 member companies from a half dozen industrial sectors involved in RM, including 43 biotechnology and pharma companies.<sup>42</sup> In April 2015, establishment of the Japan Agency for Medical Research and Development (AMED), including a Division of Regenerative Medicine Research, enabled Japan to build a centralized public research funding system for research and development, including RM.<sup>43</sup>

In the US, a major source of basic research funding for RM comes from the National Institutes of Health (NIH). It is divided among the following categories: translational research; clinical research; specific population research (wounded soldiers); and research to advance regulatory science. Over the period 2012-2014, funding from the NIH was \$2.54 billion, with an additional \$359 million for RM being invested by six other government agencies, mostly by the Department of Defense.<sup>44</sup>

### R&D Pipeline and Products

According to the Alliance for Regenerative Medicine (ARM), an advocacy organization for RM, approved RM products have been used to treat in excess of one million patients. In addition, there are several hundred thousand peer-reviewed publications, 10,000+ issued/pending patents, and well over a 100 programs in leading academic centers as well as several billion dollars in funding for research and translation spread across North America, Europe and Asia. Products in development include several hundred cell-based therapies, small molecules, biologics, tissue-engineered cells and materials and implantable devices. Additional products use cells as drug discovery or toxicity testing tools as well as clinical tools, bio-processing tools and platforms that include equipment, consumables, reagents and storage systems, according to the ARM website. Globally, there are over 700 private and 60 public companies in the RM sector (combined market capitalization of over \$10 billion). As of the 2<sup>nd</sup> quarter of 2015, there were 528 clinical trials that included RM products: 169 in phase I; 304 in phase II; and 55, in phase III. Nearly 40% of current clinical trials are in oncology while more than 10% are in cardiovascular.<sup>45</sup> To date only 30 cell and gene-based therapies have received regulatory approval in the U.S., Europe, and/or Japan (see Table III).<sup>46</sup> Around the world, companies have

faced challenges in bringing treatments to clinic. Even in the U.S., where the overall innovation environment has usually been the most favorable, Geron Corp., which started the first nation-approved trial of human embryonic stem cells, ended the program in 2011, citing research costs and regulatory complexities.<sup>47</sup>

### Regulatory Environment Complexity

In Europe, one of the challenges with regulation of advanced technologies is that they are typically developed on a small scale, in academic settings or small enterprises where regulatory compliance may be disproportionately burdensome, and EMA recognized that this was making it difficult for small and medium-sized entities (SMEs) to bring advanced therapies to market. In fact, a recent report on the ATMP regulation noted that 70% of the clinical trials being conducted in this field are by non-profits and SMEs.<sup>48</sup> In response, Europe has become the leader in developing specialized regulations in the area of cell and tissue-based therapies with its adoption of the ATMP Regulation. Other incentives included mechanisms such as fast-track assessment, fee reductions, and use of orphan drug legislation, where appropriate.<sup>49</sup>

In fact, such fast-tracking measure is the route that Japan took with its special legislation for RM (discussed earlier). In the US, FDA went in a different direction, organizing workshops on specific scientific questions, as well as using its existing authority to issue industry guidance and to designate eligible programs for expedited development and approval programs. It also provided an additional avenue for regulatory relief depending on whether product characterization met one set of criteria versus another. Under U.S. law, stem cell-based therapies, for example, would be considered “human cells, tissues, or cellular or tissue-based products” (HCT/Ps), which are defined as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.” Category Section 361 are subject only to requirements for HCT/Ps which include establishment registration and product listing, donor eligibility, and current Good Tissue Practice (cGTP), while category Section 351 are subject to additional regulation as drugs or biological products. Cell therapy, for example, would meet the definition of a drug as well as a biological product and would have to comply with cGMP standards.<sup>50</sup>

**TABLE III**

<b>Country</b>	<b>Approved Product and Related Devices</b>	<b>Manufacturer</b>
United States	ALLOCORD, HPC Cord Blood	SSM Cardinal Glennon Children's Medical Center
	Autologous Cultured Fibroblasts	Laviv (Azficel-T), Fibrocell Technologies
	Autologous Cultured Chondrocytes	Carticel, Genzyme BioSurgery
	BCG Live (Intravesical)	TheraCys, Sanofi Pasteur Limited Lic#1726
	GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen)	Organogenesis Incorporated
	Hematopoietic Progenitor Cells, Cord Blood	Hemacord, New York Blood Center
	Hematopoietic Progenitor Cell	Ducord, HPC Cord Blood, Duke University

		School of Medicine
	HPC, Cord Blood	Clinimmune Labs, University of Colorado Cord Blood Bank
	HPC, Cord Blood BLA 125432	LifeSouth Community Blood Centers, Inc.
	PROVENGE (sipuleucel-T)	Dendreon Corp.
	Apligraf (Graftskin)	Organogenesis
	OrCel	Ortec
	Dermagraft	Advanced BioHealing
	Dermagraft-TC	Advanced Tissue Science
	Epicel	Genzyme
	Integra Artificial Skin	Integra LifeSciences Corp.
	Celution	Cytori Therapeutics
	GEM 125	BioMimetic Therapeutics, Inc
	Regranex	Smith and Nephew Inc
	Infuse, Infuse bone graft	Medtronic Sofamor Danek
	Osteogenic protein-1	Stryker
Europe	Glybera	UniQure
	Chondrocelect	Tigenix
	Holoclax	Chiesi Farmaceutici
Japan	Temcell HS Inj.	Mesoblast;JCR Pharmaceuticals Co Ltd
	Heart Sheet	Terumo Corp.
	JACE® (Autologous cultured epidermis)	Fujifilm Group company Japan Tissue Engineering Co., Ltd.
	JACC® (Autologous cultured cartilage)	Fujifilm Group company Japan Tissue Engineering Co., Ltd.

Despite these efforts, RM stakeholders such as ARM, the California Institute for Regenerative Medicine (CIRM), and even the US congressional watchdog agency (GAO) have emphasized that more radical changes to the regulatory environment in Europe and the US are needed.<sup>51,52,53</sup> Among the factors contributing to the need for enhancements of current regulatory regimes are the small numbers of patients available for clinical testing of breakthrough technologies, which often involve treatments highly specific to small sub-populations of patients, or even single patients. Safety and efficacy testing of such treatments require more flexible regulatory approaches that can handle large amounts of complex data and explore multiple causal factors simultaneously, including individual patient responses, in order to ascertain

outcomes data for combinations of biochemical and molecular factors that recur in groups of patients.<sup>54</sup> The FDA Science Board summarized similar concerns in its recent report, and concluded that among the most important remedial measures needed were: new authority and increased funding to improve FDA's ability to manage new and emerging technologies, including stem cells, and advances in regulatory science that promote the lifecycle approach to regulation for drugs, devices and biologics.<sup>55</sup> Lastly, for reasons not dissimilar to the ones voiced regarding the need for adopting changes to current regulatory regimes to accommodate RM – emerging product classes posing unique regulatory challenges, regulatory frameworks in different states of maturity from region-to-region without applicable international conventions such as ICH, concerns about medical tourism based on the lack of regulatory controls – a clarion call for harmonization, or at least a so-called “regulatory convergence” of shared perspectives on standards, is being heard from many quarters.<sup>56,57,58,59</sup>

### **PROSPECTS FOR HARMONIZATION: ARE THE OBSTACLES PRACTICAL OR POLITICAL?**

Among the practical obstacles to harmonization is the fact that unmet medical needs and medical practices vary in the three major markets under discussion. Furthermore, they represent different legal jurisdictions and health care systems, with disparate regulatory and reimbursement requirements for both conventional and advanced therapies. Nevertheless, RM has broad potential to address multiple disease conditions with a variety of therapeutic modalities. The FDA has said it does not want to establish a separate pathway for RM, while the EMA and MHLW have done that albeit in ways that are similar to expediting mechanisms that FDA already has at its disposal. While the FDA can use ‘enforcement discretion’ to enforce existing regulations with more flexibility, the EU hospital exemption would probably not work because there is no state or provincial authority equivalent to Member State sovereignty. While US states have authority to regulate medical practice and facilities, they cannot regulate products that will cross state lines in commerce. Nevertheless, another regulatory innovation is progressive or adaptive licensing regimes, which allow initial market access based on preliminary data. This is essentially what Japan uses, and the FDA and EMA could modify their own versions – accelerated approval and conditional approval, respectively – to make them fit-for-purpose for RM. Even in the Ebola crisis, some urgent level of response under difficult conditions was achieved using a variety of such special programs. Perhaps it is not the practicality of legitimizing new authority that should be the focus of the debate, but rather, as both patient advocates and regulatory affairs experts have stressed, the importance of enhanced collaboration among regulatory authorities.<sup>60</sup>

There is, however, a political ambit within which regulatory agencies must operate, and often the operative factor is maintaining global competitiveness for its commercial stakeholders. Due to its size and lack of price controls, the US pharmaceutical market is the most lucrative in the world. This means that the US has an outsize influence on total world investment.<sup>61</sup> The Europeans and Japanese view their Regulatory Science initiatives as means to increase their global competitiveness. However, so far historical events have contributed to a de facto state of commercial détente. When the US Congress banned federal funding in 1995 for research on embryos—and thus the development of new stem cell lines—scientists found their work had ground to a halt. Yet scientists in Japan developed iPS cells that would eliminate the need for embryonic stem cells and allow researchers to create stem cells from the individuals who were suffering from the diseases they were studying.<sup>62</sup> At about the same time, the promising new

field of gene therapy experienced a blow from the high-profile death of an American patient in 1999 and cases of leukemia in French children a few years later. However, Europe did not abandon gene therapy and went on to further advance the field, while the U.S. retreated after the earlier setbacks.<sup>63</sup> This led to different trajectories for the primary RM therapeutic modalities in the three regions. But as big pharma increases its appetite for small-volume, high-dollar products, it remains to be seen if incipient markets for novel products like gene therapy quickly become crowded as is happening with personalized medicines for certain cancer indications. In that case, we may see a waning of the current atmosphere of biomedical business bonhomie. Nonetheless, even in the face of increasing political pressure promoting global competition, there is countervailing rationale for adopting a harmonized framework based on similar RS-driven processes for regulatory development and approval programs in order to lower R&D costs by increasing the opportunity for risk-sharing and resource-sparing collaborations across country and sector lines, and to increase market access without resort to medical tourism.

In response to RM advocacy groups and other stakeholders in Europe and the US calling for discussions on international regulatory harmonization to foster global consistency of regulatory policy, and where possible, to facilitate more rapid and efficient introduction of RM products,<sup>64,65</sup> the EMA and FDA are continuing to have that dialogue in cell and gene therapy regulators forums. Japan, for its part, is advancing a global-level regulatory science program to improve the predictability and transparency of regulatory approvals and enhancement of safety measures, and in response to calls for harmonization, will incorporate release of more information in English by PMDA, in particular through an English version of its website.<sup>66</sup> Lastly, Japan intends to build a framework for international dialogue, including with Europe and the US, to establish agreed minimum study data requirements for pre-market reviews of RM products and product quality assurance, through the efforts of its global unit within MHLW to implement Japan's International Pharmaceutical Regulatory Harmonization Strategy. Despite considerable cooperation and collaboration in holding joint meetings and ongoing discussion of technical approaches to advanced therapy evaluation among the regions through Regulators Forums,<sup>67,68,69</sup> real progress toward full regulatory harmonization, or even 'convergence' on a regulatory science approach to RM, has been slow.

Europe has been active in the area of regulatory science but is understandably focused on ironing out discrepancies among EU's member states, while Japan now turns its attention to influencing its ASEAN and other neighbors. In the US, FDA has expressed ambivalence calling regulatory science "unique but neglected,"<sup>70</sup> and lamented that while FDA recognizes the importance of RM, its funding was limited.<sup>71</sup> While Europe and Japan are making inroads in advancing RM technology, particularly in gene therapy and stem cell science, respectively, commercial viability of the sector will stay tentative without the US market, and the overall investment climate will vacillate precariously. In the US, attention is being paid to addressing new technologies, but RM is one among many – nanotechnology, bioinformatics, and precision medicine – that seem to have broader and less controversial appeal politically-speaking. Development of regenerative medicine will not advance at a pace consonant with its promise without a concurrent advance in the development of a flexible regulatory framework that facilitates innovation while integrating approaches to manage scientific uncertainty – the tools and trademark of regulatory science.

## CONCLUSION

RM is a sector with major commercial and investment opportunities as well as the potential to change the focus of medical practice from managing chronicity with “band-aid therapies” to meting out cures, with additional positive implications for achieving cost-effective and affordable health care solutions by “healing the body from within.” The field has reached an especially critical juncture in 2016 as positive findings addressing the question of whether stem cells will develop normally once transplanted into an embryo have recently been published.<sup>72, 73</sup> If replicated, these findings could have significant implications for allaying some of the safety concerns that surround stem cell research, and the clarion call by patients, practitioners, and providers for a shift from traditional to transformative medical treatment paradigms will grow more emphatic. Just as consistent and predictable regulatory frameworks founded on common principles in regulatory science provide the confidence and certainty required to bolster investment to advance the field of regenerative medicine, harmonization is essential to building that framework on a global scale. Without some determined intervention in the next few years by the public health agencies of Europe, Japan and the United States to harmonize approval pathways and risk assessment parameters, the scientific, regulatory, and funding uncertainties will continue to loom large while prospects for meaningful change will remain small on a distant horizon.

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