

COMMENTARY

The Same but Different: Regulation of Tissue Engineering and Regenerative Medicine in the Context of Regional and International Standards and Expectations

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This commentary places the contributions from several Asian–Pacific countries that constitute this Special Issue in the context of trends in global regulation of tissue engineering and regenerative medicine products and services. It concentrates on the generic issues that face regulation in each jurisdiction and the manner how these issues have to be faced in the light of cultural, political, and economic regional differences.

Commentary

ON MY FIRST VISIT TO JAPAN, well over 25 years ago, in a closed meeting at the Taniguchi Foundation, I was introduced to the phrase “the same but different,” used to convey the concept of cultural, linguistic, and other differences that get in the way of the mutual understanding of important concepts. The concepts under discussion on that occasion related to some philosophical and scientific aspects of innovative biomaterials, and my initiation into cultural differences between eastern Asia and Europe, where I was working at that time, has proved very valuable in my subsequent career. I shall use this experience in this article, where, at the invitation of Dr. Wei Liu, I provide a commentary on the articles collected in this special issue on the regulation of tissue engineering and regenerative medicine (TERM) in the Asia–Pacific region.

There can be no doubt that regulatory processes constitute one of the challenges that face the development of TERM. As the editors of this special issue have noted in their editorial, in the World Summit on Regenerative Medicine that I organized in Xi’an, China, in 2013, which addressed the key barriers to commercial and clinical success in TERM, regulation was considered to be one of the most difficult issues. Within the sphere of regulation, there are generic issues of principle and then the regional variations that influence how these principles are applied in practice.

One point that has to be recognized upfront is the fact that regulatory control in healthcare is not new; TERM is not the first sector to be brought under the scrutiny of government-mandated control. Generically, and with different modes of application, both the pharmaceutical and medical device industries have had to comply with strictures of regulatory agencies. It is important that we learn from all the positive aspects that those agencies

have brought to us, while accepting that there are many differences between the sectors and subsectors. The underlying principles of regulatory control are concerned with finding the right balances between risk and benefit and between risk and innovation. No one can doubt that, at the present time, we have very many drugs and devices that are able to treat many of the conditions of disease and trauma that we face (especially in the developed world) and the main functions of regulation and healthcare providers could simply be those of maintaining quality products (minimizing risks) and making sure that the right products reach the right patients (maximizing benefit). However, a system in which there was no innovation, through, for example, massively strict regulation over new products and therapies, could not survive in today’s political and economic environment nor would it address those conditions for which there are no effective, or possibly cost-effective, treatments.

Issues of control over the commercial development and clinical application of innovative products and services are obviously highly relevant to TERM. As the Xi’an Summit so well demonstrated, these issues involve aspects of bioethics and health economics as well as the scientific, technological, and clinical factors. With all of the powerful pharmacological and technological developments in the pharmaceutical and medical devices sectors of the past decade, we still get it wrong on many occasions, as approved drugs are shown to have unacceptable side effects after release onto the market and approved implantable devices fail, for whatever reason, to bring satisfaction to large cohorts of patients. It is not surprising that regulators, with elected politicians looking over their shoulders, and with the hype in the media extolling the potential, but as yet unproven, benefits of cell therapies and regenerative medicine, are likely to be very resistant to the widespread introduction of TERM products.

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Not surprisingly, the concept of “risk” is at the heart of the newly developing regulations for TERM, and several articles in the special issue emphasize the risk-based approach that many countries are adopting. Risk is easy to define but not so easy to analyze and manage. If a hazard is a potential source of harm, and harm is a physical injury or otherwise damage to health, then risk is usually considered as the probable rate of occurrence of a hazard causing harm and the degree of severity of the harm. With a new form of therapy, we have to consider what possible harms can arise. This is the difficult part, since we do not know the probability of, for example, tumor induction following the use of certain types of stem cells, or adverse events following significant manipulation of cells, or immune responses following the use of decellularized matrices or inflammatory responses to degrading scaffolds. This uncertainty is likely to be exaggerated by the idiosyncratic nature of host responses to therapies, with variations due to gender, age, health, and pharmacological status highly likely. There is also the huge difficulty of carrying out preclinical studies where *in vitro* and, especially, *in vivo* testing protocols have not been validated and are probably poor predictors of performance in humans. Putting all this together, we are some way off being able to analyze and manage the risks associated with TERM. Without crucial information, regulators have to rely on surrogates for risk estimates, using, as these articles show, degrees of cell manipulation, cell source details, and the presence of added biological agents as the markers of risk.

On the other side of the equation are the benefits, or potential benefits, of TERM. I have always held the view that TERM therapies should be directed at areas of the so-called unmet clinical need; that is, those conditions for which no therapies or technologies adequately address the needs of patients and their caregivers. Prospective TERM solutions for macular degeneration, type 1 diabetes, spinal cord injuries, or Parkinson’s disease would have so many benefits that the risk–benefit equation would have to be different to that where TERM is directed at conditions where good therapies and treatments are already in place. We should always bear in mind that risks of innovative therapies where alternative treatments are available include the possibility that the new method is ineffective or produces poorer outcomes than the standard of care.

The regulatory process is intimately linked to issues of health economics, where we have to be concerned with questions about the actual costs of therapies and with the systems that control reimbursements. The fact that early-stage products of tissue engineering in the United States found it so difficult to generate revenues was largely caused by the protracted process of regulatory approval, which meant that insurers were unable to pay for unapproved products, the companies having to pay all costs of clinical studies for many years. At present, business models still have not been fully developed for TERM products; indeed questions really arise over the fundamental point of whether TERM involves actual products or services, which inevitably leads to basic questions of what is it that is being regulated. Superimposed on these questions are considerations of intellectual property. Complexities of international patent law make the control of pharmaceutical agents and medical devices difficult enough; the incorporation of viable cells

and biologics into these systems within TERM can increase this complexity quite considerably.

We therefore have real challenges when considering the generic issues facing the regulation of TERM systems. The issues themselves are global in nature, but the manner in which they are addressed varies on a regional basis; it is here we see the importance of the concept of “same but different.” Some of the differences are based on demographics and disease prevalence. In countries or regions where the population is mature and increasingly moving toward domination by old people, the demand for new therapies for degenerative diseases is profound, compared to regions of lower longevity and greater poverty where infectious diseases are still prevalent and resource intensive. It would not be surprising to see different emphases on TERM regulation in these quite different communities. Cultural differences relating to the use of donated tissues and organs and the use of xenogenic materials will also have some effects.

In contrast, many emerging countries see the potential economic benefits from the high-cost-base biotechnology sectors, as mentioned by Idrus *et al.* in the contribution from Malaysia in this Special Issue, which may lead to an acceleration of the development of a regulatory infrastructure, perhaps in contrast to more developed countries where reimbursement agencies may see TERM as a financial burden.

Differences are also seen with respect to the positioning of TERM within a region’s regulatory framework. Interfaces between drugs and biologics, combination products, and medical devices vary from one jurisdiction to another, and the place for TERM has to be predicated to some extent on pre-existing processes; different presentations in this issue show that variations exist in the Asia–Pacific region in this respect. The position of biomaterial-based tissue engineering products is particularly difficult in this respect, since in some cases, as with Australia, for example, there are different regulatory homes depending on what combinations are involved.

Even though there are significant geopolitical differences in health status and healthcare industries, as summarized earlier, and even though we recognize that it would be naive to assume everyone is enthused about global harmonization of the TERM sector and its regulation, we have to continue to move toward greater convergence so that the eventual benefits of the therapies that emerge will be globally available. As noted at the beginning of this commentary, TERM is not the first healthcare area to be regulated nor is it the first to face issues of global harmonization. We should not start from the beginning but learn the lessons from these other areas, for example, from the International Medical Devices Regulators Forum; perhaps more of the same and less of the differences might help the progress of TERM.

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