

# Appropriate Governance of the Life Sciences - 3

## Regulation and Risk Governance of Stem Cell Therapies

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*This policy brief is one of a series describing Innogen's research on strategic innovation issues in life sciences, the governance and regulation of innovation and the resulting innovation trajectories determining which products are developed and which companies take the lead in developing them.*

***Stem cell science and technology promises to deliver a broad range of potential therapeutic applications***

Stem cell science and technology promises to deliver a broad range of potential therapeutic applications, particularly for chronic and degenerative diseases. Like many new areas of biomedicine, there is pressure from patient organisations to speed up development and access to new therapies. However, fundamental issues around risk and risk-governance need to be resolved before clinical trials are initiated and therapies delivered to market. This policy brief summarises some of the known and potential risks associated with stem cell therapy and considers the challenges these advanced technologies pose to regulation and risk governance in national and international contexts.<sup>1</sup>

### **BACKGROUND TO STEM CELLS AND RISK GOVERNANCE**

The stem cell field is broad and complex, and this poses significant challenges for risk assessment and governance, particularly when we are considering the development of viable therapeutic products. Difficulties arise from the variety of techniques for stem cell procurement and potential therapeutic application; the variety of sources for stem cells (embryonic, adult, foetal, umbilical cord blood and placenta), each with their own unique characteristics and risk-benefit challenges; and the different regulation and risk-governance approaches adopted by national and international agencies, which has contributed to a climate of ambiguity and uncertainty amongst innovators.

***There are a number of known and potential risks associated with stem cell therapy that need to be resolved***

In contemplating regulatory requirements for stem cell therapies, a number of known and potential risks associated with all cell therapies must be considered. First, there is the risk of human pathogen transmission or zoonoses, which could be described as a community level risk that cannot be dealt with through regulation at a local level. Scientists are trying to develop techniques, such as non-animal feeder cells, to avoid the risk of zoonoses. Second, there is a potential risk of tumorigenicity, although this is still not fully understood and requires preclinical studies. Nevertheless, because this risk is limited to the individual patient, one could argue that it is appropriate to allow the patient to accept the risk in the context of a life threatening condition with no alternative treatment regime. Third, there are risks associated with immune responses, particularly for allogeneic stem cell transplantation. This may create particular difficulties for the successful approval of clinical trials. Optimisation of immunosuppressants is therefore required for non-autologous transplantation. Finally, there may be potential for epigenetic culture effects with unknown risks to patients or presence of latent retrovirus in the cell. These risks may be considered general process risks; that is, the risk emerges in the process of development rather than in the clinic. Regulation in this case is

**Issues around risk must be resolved before clinical trials are initiated and therapies taken to market**

facility based and generally covers issues of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP). Key requirements for safe clinical trials include: the ability to stop treatment if adverse events emerge (techniques to initiate apoptosis to stop cell proliferation, for example); development of GMP quality cells; culture systems that do not require animal proteins; and development of technologies to allow better visualisation of cells in vivo.

Nevertheless, the rapid pace of the science has revealed gaps in regulation at national and international levels, particularly the lack of harmonised procedures and agreed risk-governance criteria; uncertainty around IPR and gaps engendered by borderline products that have led to diverse classification and authorisation procedures. These gaps can impact on patient access to treatment; safety and efficacy of products; as well as commercial competitiveness.<sup>2</sup> New regulatory initiatives have been proposed in both Europe and the US to deal with regulatory uncertainty.

## **NEW REGULATORY INITIATIVES IN EUROPE AND THE UNITED STATES**

### ***Europe: The Advanced Therapies Regulation***

The European Commission draft regulation on Advanced Therapies (2005) includes gene therapy, somatic cell therapy and tissue engineering. It was approved on 25 April, 2007, and is due to be enforced in all member states in 2008. Key measures include:

- The creation of a central procedure for all advanced therapies that require marketing/manufacturing authorisation, with an emphasis on quality, safety and efficacy of treatment
- The creation of a Committee for Advanced Therapies (CAT) within the European Medicines Agency (EMA) to develop new criteria and guidelines for product evaluation
- Technical and risk management requirements to ensure quality, safety, efficacy, traceability and post-marketing surveillance, in line with the US FDA system
- Incentives to support innovation in SMEs, recognising that opaque and lengthy regulatory procedures, coupled with a lack of scientific expertise in some authorities, was making it difficult for some small companies to bring products to market.<sup>4</sup>

The regulation aims to reduce the risks and uncertainties faced by innovators, although it will impose a high regulatory hurdle for safety, efficacy, quality and post-marketing surveillance. This might increase the costs and resources needed for companies to develop products, although the special incentives for SMEs may mitigate the problem. Most public sector research will be largely unaffected by the regulation, because it does not apply to clinical and pre-clinical research conducted within hospitals.

### ***United States: Developments at the FDA***

The United States has also sought to establish regulations for advanced stem cell-

**Advanced Therapies regulation aims to reduce risk and uncertainty for developers, but imposes a high regulatory hurdle for product safety**

based therapies and to create a more consistent framework for assessing safety, quality, and efficacy of the basic technologies and potential treatments. However, politics and the competing demands of various stakeholders have proven a significant challenge for the regulatory community.

Within the FDA, stem cells fall largely under the remit of CBER (Center for Biologics Evaluation and Research) and the Office of Cellular, Tissue and Gene Therapies. FDA regulates tissues on the basis of section 361 of the Public Health Safety Act, which aims to prevent the introduction, transmission, and spread of communicable diseases. Any stem cell-based product that contains cells or tissues that are highly processed, used for other than normal function, are combined with non-tissue components, or are used for metabolic purposes are subject to this Act.<sup>5</sup> Initially, the FDA proposed to approach cellular and tissue based products in terms of the quality and safety of the source and process of production, with GMP an absolute requirement. However, in 2002 the FDA's Tissue Reference Task Group decided that it is the product's 'primary mode of action' that should determine which agency takes the lead in regulation. If the primary mode of action involves direct biological activity, it is dealt with by CBER. If the product achieves its effects by structural or physiological means, such as organ replacement or tissue support system, it is regulated by the Center for Devices and Radiological Health.<sup>6</sup>

In May 2005, the FDA enacted the Good Tissue Practices and Inspection and Enforcement criteria. This covered a variety of issues, but the main focus was predominantly on stem cells that are to be used as therapies. In 2000, the FDA ruled that cell therapies from embryos or adults would be regulated as drugs, meaning that researchers would have to meet conventional standards of purity and potency. According to Rosen, stem cell research that has no immediate or stated intent for human use is not covered by the FDA. There is therefore a regulatory gap for all non-therapy driven stem cell research. The National Institutes of Health (NIH) is supposed to be responsible for non-therapeutic research, but its primary role has been to regulate federally approved human embryonic stem cell lines. For non-federally approved cell lines, regulation occurs at institutional levels, subject to local committees such as institutional review boards, animal care and use committees; and biological safety committees (Rosen, 2006, 1997). Rosen believes that a central, national review panel may be required to deal with regulatory gaps and inconsistencies engendered by devolved institutional arrangements.

The FDA Human Tissue Task Force (HTTF) - a collaborative effort of various FDA departments involved in tissue safety - was established in August 2006 to evaluate and strengthen existing systems for regulating human cells, tissues, and cellular and tissue-based products (HCT/Ps) to assess challenges in implementation of the new system and to identify any additional steps needed to further protect the public health by preventing the transmission of communicable disease while assuring the availability of safe products.<sup>8</sup>

This Task Force provides a flexible, reactive approach to emerging challenges in the regulation of cell-based therapies, where risks to public health are the primary concern. The report states: 'Because the industry is rapidly evolving, a continuing evaluation will be needed ... We also recognize that other federal partners, states, the medical community, and industry will play major roles in enhancing the safety and availability of human tissues that meet important medical needs'.

## **IMPLICATIONS OF NEW REGULATORY FRAMEWORKS FOR INNOVATION AND RISK GOVERNANCE**

*The FDA has moved from a process to product based regulatory system where the product's 'primary mode of action' determines which regulatory department is responsible*

*The FDA's Human Tissue Task Force aims to evaluate and strengthen existing risk-based systems for regulating stem cells*

***New regulatory initiatives are being developed to better facilitate both stem cell innovation and therapeutic advance***

Both Europe and the United States have made significant attempts to improve the effectiveness of the regulatory system for new cell-based therapies. Both have recognised the need to establish better institutional arrangements to evaluate safety, quality and efficacy of new products; ensure robust ethical and regulatory oversight of non-therapeutic early stage research, and at the same time support innovation in small and medium sized enterprises. Joyce Tait has highlighted the complex implications of regulatory changes on commercial and non commercial innovation strategies and processes.<sup>9</sup> Regulatory developments, especially in Europe, included consultation with a range of key stakeholders to ensure that the impact of regulation on basic science, commercial innovation and product development; and public health/safety was explicitly recognised. However, a number of important issues/questions arise about the efficiency of these new regulatory developments.

First, it is important to question whether a single, harmonised framework for the regulation of advanced therapies, including stem cells, is necessarily the best way to facilitate innovation, improve safety and efficacy; and ensure patient access to the new therapies. Furthermore, significant regulatory gaps can remain as a result of conflict between national legislation and internationally established requirements?

Second, many of the new regulatory proposals appear to include ever increasing numbers of technologies/therapies within their remit, yet many of the definitional criteria (in terms of process, product and application) are quite vague. The FDA and European regulators seem to be adopting similar approaches to cell therapies defined as medicinal products, but the regulatory systems for non-therapeutic applications seem to be more ambiguous.

Third, although the new regulations appear to establish more clear, integrated and harmonised procedures for some basic research and product development, specific criteria for evaluating the risks and benefits of different types of stem cell therapies remain largely unclear.

Finally, the regulatory distinction between therapeutic and non-therapeutic applications is important, as it creates potential for regulatory inconsistency around shared risk issues.

Europe has sought to create incentives for SMEs to develop and market new advanced therapies. Fast track regulation and orphan status may be used to favour smaller firms, but it is important to ask how these proposals might impact on the relationship between SMEs and big pharma and whether they will affect larger firm's interest in developing stem cell therapies. Indeed, high regulatory standards/requirements may increase the overall cost of R&D and patient access to new therapies. It is therefore important to get the balance right.

Although stem cell science promises to deliver many health benefits in the long term, regulatory standards are going to have to evolve to ensure treatments are safe, effective and perhaps even affordable. Issues of risk and risk-governance will significantly impact on the speed and success of commercial development. It will become increasingly important to draw on the accumulated knowledge of risks and benefits associated with tissue engineered products and cell based therapies when considering the development and governance of new stem cell products. Fair, consistent and practical regulations, which both the scientific community and industry desire, will also be crucial for attracting investment into both basic stem cell

***New regulatory frameworks will have an impact on different firms' ability to innovate and may engender new regulatory challenges***

research and downstream product development.

## NOTES

1. This brief is based on a European Commission funded project called RiskBridge, assessing risk-governance and regulation of stem cells as therapies, engaging with a range of expert stem cell scientists. We would like to thank the contributors to this project for the invaluable time, knowledge and insights they have provided.
2. See EuropaBio Industry Hearing, *Tissue Engineering and Advanced Therapies Report*, Radisson SAS Brussels, 9 November 2005, for an account of industry perspectives on this issue
3. See A. Webster 'Pan-European and Individual National Perspectives: Developing a Unified European Regulatory Approach', SATSU working Paper 29, 2006
4. See A.K. Bock & E. Rodriguez-Cerezo, 'Human Tissue-Engineered Products: Potential Socio-Economic Impacts of a New European Regulatory Framework for Authorisation, Supervision and Vigilance', European Commission Joint Research Centre, Technical Report, EUR 21838, 2005
5. See D.G. Halme & D. Kessler, 'FDA Regulation of Stem-Cell-Based Therapies', *New England Journal of Medicine*, 355, pp. 1730-1735, 2006
6. See M. Lloyd-Evans, 'Regulating Tissue Engineering', *Materials Today*, May 2004
7. M.R. Rosen, 'Are Stem Cells Drugs? The Regulation of Stem Cell Research and Development', *Journal of the American Heart Association*, 114, pp. 1992-2000, 2006
8. See FDA. *Human Tissue Task Force 2007 Report*, <http://www.fda.gov/cber/tissue/httf07report.pdf>
9. Tait, J. Multinational Company Innovation Strategies, Innogen Policy Brief

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