

REGENERATIVE MEDICINE GOVERNANCE: THE EU EXPERIENCE AND ARGENTINE POSSIBILITIES

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1. Introduction

Scholars, regulators and other key actors in the Argentine and UK regenerative medicine field have been mutually engaged for some four years now. Most recently, Fabiana Arzuaga (Arzuaga), Chair of the Argentine Advisory Commission on Regenerative Medicine & Cellular Therapies, was hosted by the ESRC Genomics Forum under its Bright Ideas Programme.¹ On 7-8 November 2011, Arzuaga and Shawn Harmon (Harmon), with support from the Genomics Forum, organised an interactive 2-day workshop with experts and scholars interested in the field (the working group). The aims of the workshop were to:

- explore the evolving regulatory state of affairs for regenerative medicine and cellular therapies in Argentina;
- report on the findings of the Governing Emerging Technologies: Social Values and Stem Cell Regulation in Argentina project;²
- draw on the experience of the UK and Europe with a view to formulating recommendations for proceeding in Argentina; and
- offer participants an opportunity to reflect on the robustness of UK and EU regulatory mechanisms.

This brief report summarises and sets out the pertinent findings of that collaborative workshop.

2. Presentations

The workshop opened with presentations from Arzuaga, Harmon and John Purvis (Purves). These contributions can be summarised as follows:

- Arzuaga reported on the Argentine political and regulatory context focusing on the period 2007 to the present. She noted that regenerative medicine research really gained momentum globally at a time when Argentina was struggling with deep economic and social crisis. Despite this, regenerative medicine and stem cell research was taken up by Argentina as a key scientific pursuit. Recent activities include CICEMA (a Stem Cell Research Consortium of 35 scientists) and the Bi-National Programme (an Argentina-

¹ See <<http://www.genomicsnetwork.ac.uk/forum/>> (accessed 05 Dec 11).

² See <<http://www.law.ed.ac.uk/ahrc/esrcvaluesproject/>> (accessed 05 Dec 11).

Brazil stem cell collaboration). However, the work of the Advisory Commission on Regenerative Medicine & Cellular Therapies has uncovered a number of problems in Argentina, including ‘stem cell tourism’ (both within Argentina and involving foreign clinics), and the unscrutinised application of (experimental) stem cell treatments to paying patients as if they were standard treatments. Professionals have responded to inquiries into these practices with the claim that what they were doing is simply ‘practise’ as opposed to ‘experimentation’. In light of this and the findings of other research, Argentine policymakers are turning their minds to definitions for the field and legislative governance options for research and clinical trials.

- Harmon reported on the empirical data generated from key Argentine stakeholders with respect to: their perceptions of the field; their ambitions for the field and its regulation; and their value concepts in relation to the field and its regulation (by government). This work – the GET: Social Values Project – exposed a clear hunger for greater and more effective engagement between researchers, regulators, and other stakeholders, including industry and publics. It uncovered and explored in detail a range of socio-moral values that stakeholders consider to be important for the regulation of the science and therefore for inclusion in regulatory instruments, either explicitly or implicitly (but unavoidably). Some of those values included knowledge-generation, honesty, transparency, democracy, solidarity, dignity, and autonomy. It was concluded that much work remains to be done on the ethico-legal front in Argentina and there is a real appetite to explore those socio-regulatory issues. Respondents felt that they (and Argentina) are at ‘a moment in time’ where important changes could truly be achieved, not least because of their confidence in the Minister of Science, Lino Baranao.
- Purves reported on the evolution of the EU medicinal products framework, which is aimed at promoting research outputs and clarifying the regulatory pathway to get products into markets. He reported that the European Commission and the European Medicines Agency (EMA) considered it important for legislators and regulators to recognise the changes that had taken place in science, legislation and the regulatory review of dossiers over recent years and the need not to inhibit the potential developments in this new area of science and medicine. This position is set out in broadly worded Regulations, technical Directives providing more specificity, and Guidelines clarifying the detail of information required to support an application for clinical trials and applications for marketing authorisations. In addition, it was recognised that regulators should be involved early so they have had some involvement with products they are asked to regulate (i.e. multiple EMA committees can engage with industry up to 3-4 years pre-product submission). Based on regulatory experience and the novel nature of future products, it was recognised in 2009

that definitions and traditional risk-based approaches needed to be rethought, and patient group interactions were important to that process because they have different tolerances for risk. Development times are typically much, much longer than anyone anticipates, and it is important for regulators to work with industry and others, including scientists, to make sure that early product classifications and development in this new area is going in the correct direction to progress towards clinical trials and marketing authorisations. With respect to cellular products, which are considered Advanced Therapy Medicinal Products (ATMPs) in Europe, clinical trials tend to be much smaller than for small molecules, which highlights the need to reflect on the benefit/risk evaluation for this class of product. Key problems are cost of the research and product development, and cost of complying with the regulation, which, in the EU, is aimed at fostering innovation. Basically, we are a long way from standardised cellular products and safety will be a key issue for their development and acceptance.

By the end of the presentations, it was agreed amongst the working group that, due to the current state of knowledge/development, many questions remain to be answered in the regenerative medicine field, including the following:

1. On what philosophy should the regulation of these products be based (i.e. what is the most optimal regulatory philosophy)?
2. What is the relevance of animal models in regenerative medicine?
3. What are the most appropriate mechanisms for shifting risk so that it is more broadly shouldered at the point of authorisation and once a product is marketed?
4. Could or should questions of efficacy be tested at least partly *after* market authorisation?

These questions are not only important for Argentina, but for Europe and beyond, and they need to be considered collaboratively across disciplines and borders.

3. Discussion

Drawing on the empirical evidence generated by the GET: Social Values Project and the specific experience of the participants, the working group undertook an open discussion around three live questions:

1. What is the impact of law on innovation, and how might law be fashioned so it avoids inhibiting innovation?

2. Is the UK/EU model for dealing with Advanced Therapy Medical Products (ATMPs) for hospital exemptions, whereby stem cell therapies can be administered to individual patients within a hospital using GMP practices, suitable for Argentina?
3. Are cellular based materials best characterised as drugs, devices, transplant tissue, or a *sui generis* substance?

With respect to the first question,³ there was much discussion. At the outset, it was agreed that perception is crucial; regulators should avoid creating the sense that the landscape is always shifting, and should strongly encourage communication (which can be appreciated and beneficial, particularly in terms of risks associated with investment). It was also noted that regulation of the science must not be overly bullish about returns. Public investment in science is about (1) idea and knowledge generation, and (2) internal investment and job creation. We should not expect any real return on the investment any time soon. Problematically, hype generates both unwarranted fears and unrealisable expectations which serve to (1) 'lock' funders in to committing further funding, and (2) increase regulatory load (despite the fact that accumulation of regulatory burden through layering of regulation stifles innovation). Hence the need to always return to first values (eg: honesty, solidarity, democracy, dignity) and first objectives (eg: quality, safety, efficacy, risk management). In Europe, there is a clear desire to adapt the regulatory environment, but there are a number of matters that need to be addressed, including suitable benefit/risk models for use in the evaluation and marketing authorisation decision-making process. Additionally, there may be some difficulty finding the right forum to design new models, and an absence of participation at the highest (and most appropriate) political levels because of a lacuna of real (and agreed) options to float. It was felt that Argentina faced a (rare) opportunity to experiment with structures and procedures so as to create the optimal regime, but in doing so, Argentina must pay attention to values, to regulatory goals (including innovation and cooperation/communication promotion), and to the resource implications (to researchers and, in particular, small and medium enterprises, which are so prevalent in the regenerative medicine setting).

On the second question,⁴ it was generally agreed that issues fundamental to the science and its regulation are: (1) producing quality; (2) achieving safety; (3) ensuring efficacy; and (4) articulating risk and equitably sharing risk responsibility and risk burden amongst the interested parties. While the EU has managed a number of matters very well (eg: encouraging cross-jurisdictional debates leading to harmonised approaches, paying attention to both supply and demand side issues, and industry-regulator-patient group discourse-based approaches to orphan drug development),

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⁴ Is the UK/EU model for dealing with Advanced Therapy Medical Products (ATMPs) for hospital exemptions, whereby stem cell therapies can be administered to individual patients within a hospital using GMP practices, suitable for Argentina?

Argentina might wish to take into account the philosophy behind the ATMP and hospital exemptions regulations in the EU in developing its own legislative regime, adapting it to the needs of its own population and structures and the wider international context. Three problems are apparent in the EU situation:

1. market access, while increasingly harmonised in the evaluation of such products, has become much less flexible;
2. expertise and decision-making for clinical trials involving multiple member states has become increasingly fragmented; and
3. regulatory certainty has been favoured over flexibility, which is important in emerging scientific fields where there is unavoidable uncertainty.

Ultimately, innovation happens at collaboration nodes, so a key regulatory goal should be the promotion of openness and interactivity in the science.

With respect to the third question,⁵ it was felt that regulators do themselves and their regulatees a disservice by focusing too much on definitions at the expense of the bigger picture. The fact is that some cellular products, if the science develops as hoped, may fall under more than one of the existing categories (boundaries are an issue), and for that reason may well be considered a *sui generis* substance. The key is to recall that the regulatory framework is aimed at making a good quality, safe and effective product that needs to be distributed through the market (within and beyond Argentina). The European approach to GMOs was to create a strict regulatory regime because nobody knew the questions that regulation should be asking, and then to streamline it as more knowledge was generated, but law is heavy and not particularly adaptable, so the detail remained and the regulations have been strengthened/toughened rather than clarified and streamlined. More usefully, the EU approach to ATMPs was quite different; it better recognised the evolution of science, the need to provide a clear pathway for products, and the goal of not inhibiting product development. A key question for emerging fields like the regenerative medicine field is to give due attention to *who* will (and should) be adapting the regulation, whether high or low level, and what process will (and should) be used so that the regime and the field actually evolve as you want them to evolve. Rather than attach labels and then build structures of regulation, it may be more fruitful to adopt a more teleological approach (i.e. envisioning and then acting to reach a desired endpoint). Regulatory foresighting can be a helpful method for doing so,⁶ and ‘lighter-touch’ or value-based regulatory regimes might also help.⁷

⁵ Are cellular based materials best characterised as drugs, devices, transplant tissue, or a *sui generis* substance?

⁶ On this point, see S Harmon, G Laurie and F Arzuaga, “Regulating for Uncertainty: The Challenges of Foresighting in New Technologies” submitted to Law, Innovation & Technology.

⁷ On this, see S Harmon, “Health Research, (Bio)Technology, Regulation and Values: Operationalising Socio-Moral Values in the Legal Setting” (2011) Innogen WP-93 available at

4. Conclusions

Experience tells us that if regulation is uncertain or leaves too much unknown, it will dissuade science innovation. The natural result of this is that policymakers often try to ‘time-proof’ regulation. But this can also stifle innovation. In the regenerative medicine field the science itself is radically uncertain. This means that regulation might best be designed as value and goal oriented and discourse-based, and that attention needs to be paid to risk, which is socially constructed and therefore changing; attention needs to be paid to what the real risks are, how they are shared, and who bears them. Ultimately, the regenerative medicine field may be an opportunity for ‘regulatory innovation’ as much as scientific innovation. Bearing that in mind, and recalling the reasonably successful regulatory approach adopted by the EU in this context, the workshop has resulted in specific recommendations being made to the Argentine Ministry of Science, Technology and Innovative Production.⁸

<http://www.genomicsnetwork.ac.uk/media/Innogen%20Working%20Paper%2093.pdf> (accessed 05 Dec 11).

⁸ See S Harmon, F Arzuaga and G Laurie, “Opinion 1:2011: Regenerative Medicine Regulation: Global Issues and Argentine Opportunities”, available at <http://www.law.ed.ac.uk/ahrc/esrcvaluesproject/reports.asp>.