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A Governance Framework for Advanced Therapies in Argentina

Regenerative Medicine, Advanced Therapies, Foresight, Regulation and Governance

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33.1 INTRODUCTION

Research in the field of regenerative medicine, especially that which uses cells and tissues as therapeutic agents, has given rise to new products called 'advanced therapies' or advanced therapeutic medicinal products (ATMPs). These cutting-edge advances in biomedical research have generated new areas for research at both an academic and industrial level and have posed new challenges for existing regulatory regimes applicable to therapeutic products. The leading domestic health regulatory agencies in the world, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have regulated therapeutic tissues and cells as biological medicines and are currently making efforts to establish a harmonised regulatory system that facilitates the process of approval and implementation of clinical trials.

In the mid-2000s, the Argentine Republic did not have any regulations governing ATMPs, and governance approaches to them were weak and diverse. Although the process of designing a governance framework posed significant challenges, Argentina started to develop a regulatory framework in 2007. After more than ten years of work, this objective was achieved thanks to local efforts and the support of academic institutions and regulatory agencies from countries with more mature regulatory frameworks. In 2019, however, Argentina was leading in the creation of harmonised regulatory frameworks in Latin America.

In this chapter I will show how the framework was developed from a position of state non-intervention to the implementation of a governance framework that includes hard and soft law. I will identify the main objectives that drove this process, the role of international academic and regulatory collaborations, milestones and critical aspects of the construction of normative standards and the ultimate governance framework, and the lessons learned, in order to be able to transfer them to other jurisdictions.

33.2 THE EVOLUTION OF REGULATION OF BIOTECHNOLOGY IN ARGENTINA: AGRICULTURAL STRENGTH AND HUMAN HEALTH FRAGMENTATION

Since its advent in the middle of the 1990s, modern biotechnology has represented an opportunity for emerging economies to build capacity alongside high-income countries, thereby blurring the developed/developing divide in some areas (i.e. it represents a 'leapfrog' technology similar to mobile phones). For this to occur, and for maximum benefit to be realised, an innovation-friendly environment had to be fostered. Such an environment does not abdicate

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moral limits or public oversight but is characterised by regulatory clarity and flexibility.[1] The development of biotechnology in the agricultural sector in Argentina is an example of this. Although it had not been a technology-producing country, Argentina faced a series of favourable conditions that allowed the rapid adoption of genetically modified crops.[2] At the same time, significant institutional decisions were made, especially with regard to biosecurity regulations, with the creation of the National Commission for Agricultural Biotechnology (CONABIA) in 1991.[3] These elements, together with the fact that Argentina has 26 million hectares of arable land, made the potential application of these technologies in Argentina – and outside the countries of origin of the technology, especially the USA – possible. This transformed Argentina into an exceptional 'landing platform' for the rapid adoption of these biotechnological developments. The massive incorporation of Roundup Ready (RR) soybean is explained by the reduction of its production costs and by the expansion of arable land. This positioned Argentina as the world's leading exporter of genetically modified soybean and its derivatives.[4]

The development of biotechologies directed at human health was more complex and uncertain, and unfolded in a more contested and dynamic setting, which resulted in it evolving at a much slower pace, with regulation also developing more slowly, involving a greater number of stakeholders. This context, as will be demonstrated below, offered opportunities for developing new processual mechanisms aimed at soliciting and developing the views and concerns of diverse stakeholders.[5]

33.3 FIRST STEPS IN THE CREATION OF A GOVERNANCE FRAMEWORK FOR CELL THERAPIES

The direct antecedent of stem cells for therapeutic purposes is the hematopoietic progenitor cell (HPC), which has been extracted from bone marrow to treat blood diseases for more than fifty years and is considered an 'established practice'.[6] HPC transplantation is regulated by the Transplant Act 1993, and its regulatory authority is the National Institute for Transplantation (INCUCAI), which adopted regulations governing certain technical and procedural aspects of this practice in 1993 and 2007.[7] This explains the rationale by which many countries – including Argentina – started regulating cell therapies under the a transplantation legal framework. However, Argentina's active pursuit of regenerative medicine research aimed at developing stem

[1] E. Da Silva, 'Biotechnology: Developing Countries and Globalization', (1998) *World Journal of Microbiology and Biotechnology*, 14(3), 463–486.

[2] There was a seed industry in the country in which national firms and subsidiaries of multinational companies actively participated as well as public institutions and had a long tradition of germplasm renewal.

[3] In 2014, the Food and Agriculture Organization (FAO) recognised CONABIA as a centre of reference for biosecurity of genetically modified organisms worldwide.

[4] E. Trigo et al., 'Los transgénicos en la agricultura argentina', (2002) *Libros del Zorzal*, I, 165–178.

[5] G. Laurie et al., 'Law, New Technologies, and the Challenges of Regulating for Uncertainty', (2012) *Law, Innovation & Technology*, 4(1), 1–33.

[6] F. Arzuaga, 'Stem Cell Research and Therapies in Argentina: The Legal and Regulatory Approach', (2013) *Stem Cells and Development*, 22(S1), 4–43.

[7] Organs and Anatomic Human Material Transplantation, Act No. 24.193, of 24 March 1993 and amendments. INCUCAI Resolution No. 307/2007 establishes the classification of medical indications for autologous, allogeneic and unrelated transplantation of HPC. It also regulates procedures for tissue banking, including the banking of stem cells from umbilical cord blood (UCB), which is an alternative source of HPC used in transplants in replacement of bone marrow.

cell solutions to health problems required something more, and despite its efforts to promote this research, there were no regulations or studies related to ethics and the law in this field.[8]

In 2007, the Advisory Commission on Regenerative Medicine and Cellular Therapies (Commission) was created under the National Agency of Promotion of Science and Technology (ANPCYT) and the Office of the Secretary of Science and Technology was transformed into the Ministry of Science, Technology and Productive Innovation (MOST) in 2008.[9] The Commission comprised Argentinian experts in policy, regulation, science and ethics, and was set up initially with the objective of advising the ANPCYT in granting funds for research projects in regenerative medicine.[10] However, faced with a legal gap and the increasing offer of unproven stem cells treatments to patients, this new body became the primary conduit for identifying policy needs around stem cell research and its regulation, including how existing regulatory institutions in Argentina such INCUCAI and the National Administration of Drugs, Food and Medical Technology (ANMAT), would be implicated.

The Commission promoted interactions with a wide range of stakeholders from the public and private sectors, the aim being to raise awareness and interest regarding the necessity of forging a governance framework for research and products approval in the field of regenerative medicine. In pursuing this ambitious objective, the Commission wanted to benefit from lessons from other regions or countries.[11] In 2007, it signed a Collaborative Agreement between the Argentine Secretary of Science and Technology and the University of Edinburgh's AHRC SCRIPT Centre (the Arts and Humanities Research Council Research Centre for Studies in Intellectual Property & Technology Law).[12] This collaboration, addressed in greater detail below, extended to 2019 and was a key factor in the construction of the regulatory framework for ATMPs in Argentina.

33.4 FROM TRANSPLANTS TO MEDICINES

In 2007, in an attempt to halt the delivery of untested stem cell–based treatments that were not captured by the current regulatory regime applicable to HPCs, the Ministry of Health issued Resolution MS 610/2007, under the Transplant Act 1993. The 610/2007 Resolution states 'activities related to the use of human cells for subsequent implantation in humans fall within the purview of the Transplant Authority (INCUCAI)'.[13] This Resolution formally recognises INCUCAI's competence to deal with activities involving the implantation of cellular material

[8] S. Harmon, 'Emerging Technologies and Developing Countries: Stem Cell Research (and Cloning) Regulation and Argentina', (2008) *Developing World Bioethics*, 8(2), 138–150.

[9] National Agency of Promotion of Science and Technology, which in 2008 became the Ministry of Science, Technology and Productive Innovation (MOST).

[10] Resolution ANPCYT Nº 214/06 creates the Advisory Commission in Cellular Therapies and Regenerative Medicine with the objective to advise the National Agency of Promotion of Science and Technology in the evaluation of research projects in regenerative medicine (RM) that request funding for research as well as to study regulatory frameworks on RM in other jurisdictions.

[11] S. Harmon and G. Laurie, *The Regulation of Human Tissue and Regenerative Medicine in Argentina: Making Experience Work. SCRIPT Opinions, No. 4* (AHRC Research Centre for Studies in Intellectual Property and Technology Law, 2008).

[12] AHRC/SCRIPT was directed by Professor Graeme Laurie.

[13] The direct antecedent of the use of stem cells for therapeutic purposes is the hematopoietic progenitor cells (HPC) transplantation from bone marrow to treat blood diseases. This practice has been performed for more than fifty years and is considered an 'established practice'. HPC transplantation is regulated by the Transplant Act 1993, and its regulatory authority is INCUCAI, which has issued regulations governing certain technical and procedural aspects of this practice. INCUCAI Resolution 307/2007 establishes the classification of medical indications for autologous, allogeneic and unrelated transplantation of HPC. It also covers procedures for tissue banking, including the banking

into humans. However, it is very brief and does not specify which type of cell it applies to, nor any specific procedures (kind of manipulation) to which cells it can be subject, an issue that is, in any event, beyond the scope of the Act.[14] This Resolution is supplemented by Regulatory Decree 512/95, which, in Article 2, states that 'any practice that involves implanting of human cells that does not fall within HPC transplantation is radically new and therefore is considered as experimental practice until it is demonstrated that it is safe and effective'.

To start a new experimental practice, researchers or medical practitioners must seek prior authorisation from INCUCAI by submitting a research protocol signed by the medical professional or team leader who will conduct the investigation, complying with all requirements of the regulations, including the provision of written informed consent signed by the research subjects, who must not be charged any monies to participate in the procedure. In May 2012, INCUCAI issued Resolution 119/2012, a technical standard to establish requirements and procedures for the preparation of cellular products. Substantively, it is in harmony with international standards of good laboratory and manufacturing practices governing this matter. However, very few protocols have been filed with INCUCAI since 2007, and the delivery of unproven stem cell treatments continued to grow, a situation that exposed INCUCAI's difficulties in policing the field and reversing the growth of health scams.[15]

Another attempt to regulate was the imposition of obligations to register some cellular-based products as biological medicaments. The ANMAT issued two regulations under the Medicines Act 1964:[16] Dispositions 7075/2011 and 7729/2011. These define 'biological medicinal products' as 'products derived from living organisms like cells or tissues', a definition that captures stem cell preparations, and they are categorised in both Dispositions as ATMPs. Cellular-based or biological medicaments must be registered with the National Drugs Registry (REM), and approval for marketing, use and application in humans falls within the scope of the Medicines Act and its implementing regulations. Cellular medicine manufacturers must register at the ANMAT as manufacturing establishments, and they must request product registration before marketing or commercialising their products.

Importantly, the ANMAT regulations do not apply in cases where ATMPs are manufactured entirely by an authorised medical centre, to be used exclusively in that centre. In that case, the local health authority maintains the right for approval. Like all regulations issued by the national Ministry of Health under the Medicines Act, the provisions of Dispositions 7075/2011 and 7729/2011 apply only in areas of national jurisdiction, in cases where interprovincial transit is implicated, or where ATMPs are imported or exported. In short, the Medicines Act is not applicable so long as the product does not leave the geographic jurisdiction of the province. And within the provinces, regulatory solutions were inconsistent; for example, in one they were regulated as transplants and in another as medicines.

As alluded to above, while imperfect regulatory attempts were pursued, the offer of unproven treatments with cells continued to grow. As in many countries, it was usual to find publications in the media reporting the – almost magical – healing power of stem cells, with little or no

of stem cells from umbilical cord blood (UCB), which is an alternative source of HPC used in transplants in replacement of bone marrow.

[14] Arzuaga, 'Stem Cells Research in Argentina'.

[15] In eleven years, Incucai has approved four research protocols using outologous cells. Details of protocols can be accessed on: 'Tratamientos existentes', (Ministerio de Cliencia, Tecnología e Innovación Productiva, Presidencia de la Nación), www.celulasmadre.mincyt.gob.ar/tratamientos.php.

[16] Commercialization Regime of Medicinal Products Act, Act 16.463, of 8 August 1964, and Decree 9763/1964 and amendments.

supporting evidence, and such claims have great impact on public opinion and on the decisions of individual patients. Moreover, the professionals offering these 'treatments' took refuge in the independence of medical practice and the autonomy that it offers, but it seems clear that some of the practices reported were directly contrary to established professional ethics, and they threatened the safety of patients receiving the treatments.[17] In addition to the safety issues, given that these were experimental therapies (that have not been proven to be safe and effective), health insurers have stated their refusal to cover them (and one can anticipate the same antipathy to indemnifying patients who chose to accept them and are injured by them). Indeed, patients filed judicial actions demanding payment of such treatments by both health insurance institutions and the national and provincial state (as guarantors of public health).[18]

The regulatory regime – by virtue of its silence, its imperfect application to regenerative medicine and concomitant practices, and its shared authority between national and provincial bodies – permitted unethical practices to continue, and decisions of some courts have mandated the transfer of funds from the state (i.e. the social welfare system) to the medical centres offering these experimental cellular therapies. In short, the regime established a poorly coordinated regulatory patchwork that was proving to be insufficient to uniformly regulate regenerative medicine – and stem cell – research and its subsequent translation into clinical practice and treatments as ATMPs. Moreover, attempts by regulatory authorities to stop these practices, though valiant, also proved ineffective.

33.5 KEY DRIVERS FOR THE CONSTRUCTION OF THE GOVERNANCE FRAMEWORK

The landscape described above endured until 2017, when the Interministerial Commission for Research and Medicaments of Advanced Therapies (Interminsterial Commission) was created. This new body, jointly founded by the Ministry of Science and Technology (MOST) and the Ministry of Health (MOH), which also oversaw INCUCAI and ANMAT, was set up to:

1. Advise the MOST and MOH in the subjects of their competence.
2. Review current regulations on research, development and approval of products in order to propose and raise for the approval of the competent authority, a comprehensive and updated regulatory framework for advanced therapies.
3. Promote dissemination within the scientific community and the population more broadly on the state of the art relating to ATMPs.

Led by a coordinator appointed by the MOST, the Interministerial Commission focused its efforts first on adopting a new regulatory framework that was harmonised with the EMA and FDA, and that recognised the strengths of local institutions in fulfilling its objectives. The

[17] C. Krmpotic, 'Creer en la cura. Eficacia simbólica y control social en las prácticas del Dr. M.,' (2011) *Scripta Ethnológica*, (XXXIII), 97–116.

[18] The National Constitution of Argentina establishes a right to health, and stipulates that the private or public health system of the provinces or federal authorities is guarantor of the right. The following are examples of judicial cases that were reported by the Legal Department of OSDE (Social Security Organization for Company Managers): 'Jasminoy, María Cristina c / Osde Binario s /Sumarísimo' (Expte. 4008 / 03), Court of First Instance in Civil and Commercial Matters No. 11, Secretariat No. 22. The treatment was covered by OSDE. Diagnosis: Multiple Sclerosis; 'Silenzi de Stagni de Orfila Estela c / Osde Binario S. A s / Amparo' (Expte. 4475 / 05), National Civil Court No. 11. The treatment was covered by OSDE. Diagnosis: Multiple Sclerosis; 'Ferrreira Mariana c / Osde Binario y otros / Sumarísimo' (Expte. 8342 / 06), Civil and Commercial Federal Court No. 9, Secretariat No. 17. The court decision ordered the coverage of the treatment but it could not be implemented because the plaintiff died. Diagnosis: Leukaemia.

strategy to create the governance framework was centred in three levels of norms: federal law, regulation and soft law. The proposal was accepted by both Ministries and efforts were made to put in force, first, the regulatory framework and soft law in order to stop the delivery of unproven treatments. These elements would then be in force while a bill of law was sent to the National Parliament.

On September 2018, the new regulatory framework was issued through ANMAT Disposition 179/2018 and an amendment to the Transplant Law giving competence to INCUCAI to deal with hematopoietic progenitor cells (CPH) in their different collection modalities, the cells, tissues and/or starting materials that originate, compose or form part of devices, medical products and medicines, as well as cells of human origin of autologous use used in the same therapeutic procedure with minimal manipulation and to perform the same function of origin.

The Interministerial Commission benefitted immensely from the work of the original Commission, which was formed in 2007 and which collaborated across technical fields and jurisdictional borders for a decade, moving Argentina from a position of no regulation for ATMPs, to one of imperfect regulation (limited by the conditions of the time). The original Commission undertook the following:

1. Undertaking studies on the legislation of Argentina and other countries to better understand how these technical developments might be shaped by law (i.e. through transplant, medicines or a *sui generis* regime).
2. Proposing a governance framework adapted to the Argentine legal and cultural context, harmonised with European and US normative frameworks.
3. Communicating this initiative to all interested sectors and managing complex relationships to promote debate in society, and then translate learnings from that debate into a normative/governance plan.[19]

The work of the Commission was advanced through key collaborations; first and foremost with the University of Edinburgh (2007–2019). This collaboration had several strands and an active institutional relationship.[20]

Other collaborations involved the Spanish Agency for Medicaments, the Argentine judiciary[21] and the creation of the Patient Network for Advanced Therapies (APTA Network) to provide patients with accurate information about advances in science and their translation into healthcare applications. All this was accompanied by interactions with a range of medical societies in order to establish a scientific position in different areas of medicine against the offer of unproven treatments.[22]

[19] V. Mendizabal et al., 'Between Caution and Hope: The Role of Argentine Scientists and Experts in Communicating the Risks Associated with Stem Cell Tourism',(2013) *Perspectivas Bioéticas*, 35–36, 145–155.

[20] An ESRC-funded research project, *Governing Emerging Technologies: Social Values in Stem Cell Research Regulation in Argentina*, explored various stakeholders' regulatory values, ambitions and tolerances. The institutional relationship resulted in the training of researchers and members of the Commission, the hosting of eight international seminars at which experts from various countries – mainly the UK – shared their experiences, and the holding of fellowships which facilitated research visits to academic and regulatory institutions in the UK.

[21] Which resulted in engagement activities with judicial associations so as to raise awareness among judges about the problem of experimental treatments, and the need to avoid ordering the transfer of resources from the health system to unscrupulous medical doctors

[22] See more at: 'Red argentina de pacientes', (Argentina.gob.ar), www.argentina.gob.ar/ciencia/celulasmadre/red-argentina-de-pacientes.

33.6 CURRENT LEGAL/REGULATORY FRAMEWORK

The current legal framework in force and proposed by the Interministerial Commission is the result of a collaboration work focused on identifying the different processes involved in research and approval of ATMPs and set up an effective articulation between its parts. It consists of laws and regulations and establishes a coordinated intervention of both authorities, ANMAT and INCUCAI, in the process of approval of research and products. The system operates as follows:

1. Medicaments Law establishes ANMAT with competence to regulate the scientific and technical requirements at national level applicable to clinical pharmacology studies, the authorisation of manufacturing establishments, production, registration and authorisation of commercialisation, and surveillance of Advanced Therapy Medicaments.[23]
2. Transplants Law establishes INCUCAI with competencies to regulate the stages of donation, obtaining, and control of cells and/or tissues from human beings when they are used as starting material in the production of an ATMP.[24]
3. Manufacturing establishments that produce ATMP must be authorised by ANMAT.
4. When an ATMP is developed and used within the same facility, the donation, procurement, production and control stages are ruled under the INCUCAI regulations. INCUCAI must request the intervention of ANMAT for the evaluation and technical assistance in the stages of the manufacturing process, in order to guarantee that they meet the same standards as the rest of the Advanced Therapy Medications.
5. Cell preparations containing cells of human origin with minimal manipulation are not considered medications and will be under the INCUCAI regulations.

Finally, the newly amended Argentine Civil Commercial Code 2015 establishes the ethico-legal requirements for clinical trials. Specifically, Article 58 states that investigations in human beings through interventions, such as treatments, preventative methods, and diagnostic or predictive tests, whose efficacy or safety are not scientifically proven, can only be carried out if specific requirements are met relating to consent, privacy, and a protocol that has received ethical approval, etc.

Laws and regulations above described combine to form a reasonably comprehensive normative system applicable to research, market access approval and pharmacovigilance for ATMPs, harmonised with international standards.

Importantly, and interestingly, though many stakeholders in the period 2011–2017 reported a preference for command-and-control models of regulation (i.e. state-led, top-down approaches)[25] and many elements of the prevailing regime do now reflect this, the framework itself emerged through a bottom-up, iterative process, which sought to connect abstract concepts and models of governance with actual experience and the national social and legal normative culture. While the Commission, together with a key circle of actors, shaped the process, a wide variety of stakeholders from academia, regulatory bodies, medical societies, researchers, patients

[23] ANMAT Disposition 179/2018.

[24] Law No. 27.447/2018 y su Decreto Reglamentario No. 16/2019.

[25] S. Harmon, 'Argentina Unbound: Governing Emerging Technologies: Social Values in Stem Cell Regulation in Argentina', (2008) Presented at *European Association of Health Law, 'The Future of Health Law in Europe' (Conference, 10–11 April 2008, Edinburgh)*.

and social media cooperated to advance the field. Their efforts were very much an example, imperfectly realised, of legal foresighting.[26]

To complete the normative framework currently in force, it would be advisable to maintain a soft law design to provide support to regulatory bodies to maintain updated proceedings as well as the flexibility to accompany the advances of science. Finally, it would be prudent to count on a federal law that regulates clinical research, and fundamentally to provide the regulatory authority a robust policy power to stop the advance of eventual unproven treatments across the country as a legal warranty for the protection of patients and research human subjects.

33.7 CONCLUSION

The design and adoption of a governance framework for regenerative medicine research and ATMPs in the Argentine Republic has been a decade-long undertaking that has relied on the strengths and commitment of key institutions like MOST, MOH, ANMAT and INCUCAI and on the ongoing engagement with a range of stakeholders.

To achieve the current normative framework, it was necessary to amend existing legal instruments and issue new laws and regulations.

The new framework exemplifies a more joined-up regime that is harmonised with other important regulatory agencies like EMA and the FDA. This is important because the development of ATMPs is increasingly global in nature, and it is expected that Argentine regulators will work closely with international partners in multiple ways to support safe and effective innovation that will benefit a wider segment of the population, including, importantly, traditionally marginalised groups.

[26] G. Laurie et al., 'Foresighting Futures: Law, New Technologies, and the Challenges of Regulating for Uncertainty', (2012) *Law, Innovation and Technology*, 4(1), 1–33.

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