Addressing the limitations of the regulatory landscape in South Africa regarding advanced cell and gene therapies and related sectors involving human cells, tissues and organs

I M Viljoen, BPharm; **M S Pepper**, MB ChB, PhD

Institute for Cellular and Molecular Medicine, and SAMRC Extramural Unit for Stem Cell Research and Therapy, Faculty of Health Sciences, University of Pretoria, South Africa

Corresponding author: *M S Pepper (michael.pepper@up.ac.za)*

Advanced cell-based and gene therapy products emerged during the 1990s as new health product categories for treating and curing previously untreatable or incurable conditions. These products are complex, diverse and therapeutically specific, requiring specialised regulatory frameworks. During the last three decades, several jurisdictions have constructed specific regulatory frameworks to ensure these products' safety, clinical efficacy and quality. As these are new and disruptive products, these frameworks are continuously evolving. However, South Africa (SA)'s regulatory frameworks for medicines, human biological materials and genetically modified organisms have not kept pace with scientific and technological developments, leaving regulatory gaps. We briefly describe these novel products and their regulatory frameworks, and propose a way forward in SA.

Keywords: advanced cell-based products, gene therapies, regulatory frameworks, South Africa, Medicines and Related Substances Act, National Health Act

S Afr Med J 2025;115(1):2629. https://doi.org/10.7196/SAMJ.2024.v115i1.2629

Advanced cell-based products are a diverse category of manufactured products that consist of or contain viable cells as their active components. Their starting materials are cells and tissue types from different sources. These products exert their therapeutic effect through the pharmacological, immunological, or metabolic action of cells, or structural properties of tissues. The cells may be expanded to increase their numbers, induced to change their biological or structural properties, combined with other cells into complex tissues or combined with other substances, materials, or devices, or cells may be genetically modified.

Gene therapies contain therapeutic nucleic acids that regulate, repair, replace, add to, or delete a defective genetic sequence. Gene therapies can be divided into *in vivo* and *ex vivo* gene therapy products. For *ex vivo* gene therapies, nucleic acids are transferred *in vitro* into somatic cells, including stem cells (the *ex vivo* genetic manipulation of germ cells is internationally prohibited), before the cells are introduced into the patient's body. In contrast, *in vivo* gene therapies use vectors to introduce nucleic acids directly into a patient's body to cure inherited genetic disorders.

One must distinguish between gene therapies that modify somatic cells, such as haematopoietic stem and progenitor cells, to correct inherited genetic disorders, such as sickle cell disease, and adoptive cell therapy (ACT) products where differentiated T-cells, natural killer (NK) cells and macrophages are genetically modified to direct and enhance their immunogenicity.

Substantial processing of the cells or tissues distinguishes them from minimally processed cells or tissues for transplantation. Several factors separate advanced cell-based products from conventional medicines. Table 1 highlights some of these factors.

What are regulatory frameworks?

Governments must protect their citizens' health, safety and interests. To achieve this, they have established regulatory frameworks to (*i*) ensure the safety, clinical efficacy and quality of medicines and other health products; (*ii*) protect the dignity and safety of the donors of the human biological material, as well as recipients and their offspring; and (*iii*) ensure that genetically modified organisms do not cause harm to people or the environment.

These frameworks consist of Acts of Parliament establishing broad regulatory principles, and providing for their legal basis. Acts empower ministers to promulgate regulations required to implement specific sections of the Acts. They also establish regulatory authorities to implement and enforce the Acts and regulations (statutes). Policies, guidelines and standards can augment the framework, and while these are generally not legally binding, regulators and courts can use them to determine compliance with a law. The standards and guidelines can also become binding by incorporating them into regulations. As regulatory frameworks are constructed on jurisdiction-specific statutes, they are specific to that jurisdiction. However, guidelines and standards can be agreed upon across jurisdictions to facilitate trade. Table 2 shows an overview of this hierarchy.

In South Africa (SA), the Bill of Rights in the Constitution[1] lays the foundation for all legislation. It enshrines the rights of all the country's people to dignity (s10), equality (s9) and freedom (s12), and binds the legislature, the executive, the judiciary and all state organs (s8). Section 24(a) grants the right to an environment that does not harm people's health or wellbeing, and section 27(1)(a) grants the right to access healthcare services, while section 27(2) obligates the state to realise this right progressively.[1]

Table 1. Factors separating advanced cell-based products from conventional medicines

Factor	Advanced cell-based products	Conventional medicines
Nature of product	Living biological entities (cells, tissues).	Chemical compounds (small molecules, biomolecules).
Starting material	Source: highly complex and diverse autologous (self), allogeneic (donated), xenogeneic (other species) cells or established cell lines. Autologous cells and tissue are collected from patients and may be variable in quality. Allogeneic cells are subject to donor selection, testing, collection, processing, storage and distribution requirements. Type: Embryonic or induced pluripotent stem cells, somatic tissue stem and progenitor cells or terminally differentiated cells.	Relatively standardised chemical raw materials and substances.
Active component of ingredient (drug substance)	Process: complex, often involves multiple steps, including cell selection, induction, culture, differentiation and purification. Scale: mostly custom-prepared for individual patients.	Typically involves standardised chemical synthesis or fermentation processes. Mass produced as bulk off-the-shelf substances.
Final product (drug product)	In most cases, final product is the fresh or preserved active component.	Formulated with excipients into dosage forms.
Shelf life	Ultra-short due to the living biological nature of the cells of tissues.	Months to years depending on storage conditions.
Complexity	High, due to the biological nature of the product (cells contain thousands of different but interacting molecules).	Lower, due to the chemical nature of the product.
Quality control	Challenging, due to the scarcity and cost of inter-product diversity and ultra-short shelf life, the product and the condition of the patient.	Easier, often involves identification, purity and potency testing.
Regulatory framework	Novel patient-focused, risk-based frameworks.	Regulated under routine internationally harmonised pharmaceutical paradigm for commercial medicines.
Target diseases	Complex, rare and immediately life-threatening diseases that are difficult to treat with conventional medicines.	Can target a wide range of diseases.
Clinical trials	Always in patients. Non-conventional trial designs. Often *n*=1 trial under umbrella protocols. Registries and meta-analysis of outcomes.	Conventional phased approach. Highly powered, large scale multi-centre comparator trials to show incremental benefits over established treatments.
Commercial market potential	Relatively low due to limited patient numbers.	Relatively high, but may be limited by generic competition.
Challenges	Patient access, availability, cost reduction, scale-up.	Manufacturing costs, intellectual property and market competition.

Table 2. Legislation overview

Level	Binding	Existing legislation
Constitution	Yes	Yes
Policy	No	Limited
Act	Yes	Yes
Regulations	Yes	Incomplete
Guidelines/standards	No	None officially

These and other sections of the Bill of Rights form the constitutional basis for the Medicines and Related Substances Act 101 of 1965 (Medicines Act),[2,3] the National Health Act 61 of 2003 (NHA)[4] and the Genetically Modified Organisms Act 15 of 1997 (GMO Act).[5] These Acts and their regulations, in turn, provide the legal bases for SA's medicine, human biological material (HBM) and GMO regulatory frameworks. Table 3 lists these selected SA Acts, and Table 4 the regulations to chapter 8 of the NHA.

In rapidly developing technological environments, regulatory frameworks must constantly evolve. They should be robust regarding their values, but flexible enough not to stifle progress and development.

Medicines regulatory frameworks and regulatory authorities

National medicines regulatory frameworks were constructed during the 1960s in response to the thalidomide tragedy, and medicines regulatory authorities (MRAs) were established to ensure that industrially manufactured commercial medicines are safe, clinically effective and manufactured in suitable facilities with adequate controls. However, regulatory authorities are not created equally. At one end of the spectrum, narrowly focused regulators such as the European Medicines Agency (EMA) focus only on industrially manufactured medicinal products for commerce between European Union (EU) member states. The EU uses the term 'medicinal products', which includes small-molecule medicines, biopharmaceutical molecule-

Table 3. Selected South African Acts and regulations

Instrument	Date	Description
Bill of Rights[1]	18 December 1996	Chapter 2, Bill of Rights of the Constitution of the Republic of South Africa, 1996 (Act No. 108 of 1996) (Bill of Rights)
Act 101 of 1965[3]	8 January 2016	Medicines and Related Substances Act No. 101 of 1965 (as amended)
Act 101 regulations[6]	25 August 2017	General Regulations to Medicines and Related Substances Act of 1965
Act 61 of 2003[4]	23 July 2004	National Health Act No. 61 of 2003 (as amended)
Act 61 chapter 8 regulations	2 March 2012	Government Gazette no. 35099.
Act 15 of 1997[5]	20 May 1997	Genetically Modified Organisms Act (Act 15 of 1997) (as amended)
Act 15 regulations[7]	26 February 2010	Regulations to the Genetically Modified Organisms Act of 2010

Table 4. Regulations to chapter 8 of the National Health Act 61 of 2003

Number	Title	Pages
R 177[8]	Regulations relating to the use of human biological material	31 - 38
R 179[9]	Regulations relating to blood and blood products	62 - 74
R 180[10]	Regulations regarding the general control of human bodies, tissue, blood, blood products and gametes	75 - 96
R 181[11]	Regulations relating to the import and export of human tissue, blood, blood products, cultured cells, stem cells, embryos, foetal tissue, zygotes and gametes	97 - 124
R 182[12]	Regulations relating to tissue banks	125 - 141
R 183[13]	Regulations relating to stem cell banks	142 - 158

Table 5. Professional bodies and self-regulation

Area	Professional body	Guidelines/standards
Transplantation	Southern African Transplantation Society	Yes. http://www.sats.org.za/Guidelines.asp
Assisted reproductive technology	Southern African Society of Reproductive Medicine and Gynaecological Endoscopy	Yes. http://www.fertilitysa.org.za/TreatmentGuidelines/ReproductiveMedicine.asp
Blood and blood products	National Blood Committee (not in operation since 2008)	Yes. Standards for the Practice of Clinical Guidelines for the Use of Blood Products in South Africa (5th edition 2014), South African National Blood Transfusion Service
Cell-based therapy	South African Stem Cell Transplantation Society	Yes. http://www.stemcell.org.za/index.htm
Genetic services	Southern African Society of Human Genetics	Yes. http://www.sashg.org/documents.htm
Tissue banks	South African Tissue Bank Association	Yes. https://satiba.org.za
Forensic pathology and medicine	National Forensic Pathology Services Committee	Yes. No website
	National Clinical Forensic Committee	In progress

based medicines, medical devices that include medicinal products and industrially manufactured advanced therapy medicinal products (ATMPs).[14,15] At the same time, national MRAs remain responsible for products intended for use or sale only in that member state.

At the other end of the spectrum are regulators with broad regulatory mandates, such as the US Food and Drug Administration (FDA) and Australia's Therapeutic Goods Administration (TGA), which regulate a wide range of products that could affect human health. The US Federal Food, Drug and Cosmetic (FD&C) Act[16] mandates the FDA to regulate drugs and medical devices. However, the Public Health Services (PHS) Act places regulation of biological products (42 CFR 351)[17] and preventing the transmission of communicable diseases through transfusion or transplantation (42 CFR 361)[18] under the FDA mandate. Prescription drugs, including biopharmaceutical molecule-based products manufactured through biological processes, are regulated by the Center for Drug Evaluation and Research.

Changing mandates

When the need to regulate blood, blood components, plasma-derived medicinal products (PDMPs), gene therapies and advanced cell-based products arose, the FDA recognised that the existing regulatory frameworks for drugs, biological products and medical devices were inadequate, and constructed new regulatory frameworks for blood, blood components, PMDPs,[19] human cells and tissues and human cell and tissue-based products.[20] These biologics are regulated by the Center for Biologics Evaluation and Research. Notably, the regulation of gene therapies and gene-modified cell products for humans falls under the FDA's jurisdiction, and is outside the scope of agricultural GMO regulation.

The Australian TGA also differentiates between biological products such as vaccines and *in vivo* gene therapy products as prescription medicines, and products containing living human cells including *ex vivo* gene-modified cells, as biologics.[21]

In the EU, blood and blood components, human cells and tissue for transplantation are generally regulated by separate competent authorities in each member state, albeit following centralised EU regulations.[22] However, in Germany, the Paul Ehrlich Institute regulates biopharmaceuticals, ATMPs used only in Germany, blood products, haematopoietic stem and progenitor cell preparations and tissue preparation for transplantation.

Several other countries and jurisdictions have constructed specific advanced therapeutic product regulatory frameworks for the past two decades.[15,23-25] SA's regulatory framework has not kept pace with scientific developments, which has resulted in significant regulatory gaps.

Changing roles

While the initial roles of MRAs were to ensure the safety, clinical efficacy and quality of medicines, their mandates have been expanded to include bio- and radiopharmaceuticals, gene therapies, medical devices and *in vitro* diagnostics, blood, blood components, plasma-derived medicinal products and vaccines, cell and tissue preparations, and advanced cell- and tissue-based products. In the USA, acts like the Food and Drug Administration Modernisation Act of 1997,[26] the 21st Century Cures Act of 2016[27] and the Food and Drug Omnibus Reform Act of 2022[28] significantly changed the FDA's role. Similarly, in Japan, the Regenerative Medicine Promotion Act[23] and the Act on Ensuring the Safety of Regenerative Medicine[24] have resulted in a comprehensive review of the Pharmaceuticals and Medical Devices Act.[25] Regulators' roles have also expanded into regulating basic research, providing advisory support to researchers and product developers and providing financial support to micro, small and medium-sized enterprises and activities to support the development of products for rare diseases and paediatric use through regulatory incentives.

Changing environment

Like other industries, the pharmaceutical industry is profit-driven, and its primary purpose is to deliver profits to its shareholders. The original purpose of regulatory authorities was to protect patients by ensuring that industrially manufactured commercial pharmaceutical products are safe and effective. Harmonisation efforts in Europe and internationally were mainly designed to improve market access for pharmaceutical companies. However, these profit-driven companies fail to address the unmet medical needs of small numbers of patients with rare diseases, or patients in low-value markets. Academic research institutions and non-profit organisations are increasingly addressing these needs. This is especially true for advanced cell-based and gene therapy products, necessitating regulatory authorities to construct specific regulatory frameworks for academic and non-profit organisations to provide appropriate levels of patient protection.

Advances in manufacturing technologies now make it possible to manufacture individualised products at the point of care in automated closed systems. These processes must be adaptable to compensate for variable patient-specific starting materials, and release criteria for final products may be flexible. This also requires the availability of specific qualified facilities and staff with skillsets that diverge from the classic skills expected in pharmaceutical manufacturers. This requires new ways of thinking about technology transfer, critical quality attributes, critical process parameters and product release criteria.

The South African situation

South and southern Africa have high levels of genetic diversity. This is seen in various country- and region-specific genetic diseases, making this one of the most exciting places in the world to conduct biomedical research. However, these diseases place a considerable burden on individuals, families, communities and society in general. Addressing these needs requires a regulatory framework that ensures patient safety and supports patient access to novel and disruptive treatments.

SA has a burden of communicable and non-communicable diseases and traumatic injuries that advanced cell-based products can address. This includes ACT products that can be used to treat chronic infectious diseases or cancers, and engineered tissue products to repair burns and other traumatic injuries, or to address diseases such as diabetes. This in turn requires a specific regulatory framework for health products that use human or animal biological materials as starting materials. There is a discontinuity between the regulatory frameworks for human biological materials for transfusion or transplantation, and human biological materials used as starting materials for medicines and medical devices. A regulatory framework for advanced cell-based products is absent.

A proposed way forward

The authors believe that two work streams need to run concurrently. The first is to work within the existing legislative environment's boundaries, and apply principles of international best practice where there is no guidance. The second is to undertake a critical review of current legislation, and intentionally and prospectively plan for a well-co-ordinated process to ensure that we produce an appropriate and well-balanced regulatory structure for the future.

Regarding the first work stream, the Minister of Health may promulgate legally binding regulations after consultation. Thus, the minister can promulgate, after consultation, interim regulations in the form of *lex specialis* for regulating blood, blood components, plasma-derived medicines, advanced cell-based products and gene therapies. This is feasible as the current Medicines Act and NHA and their regulations fall under the minister's authority.

The starting point for the second workstream should be the creation of a carefully considered strategic overview of the existing legislation, and understanding how the affected areas can be partitioned to make the required overhaul more manageable. This will allow for the creation of specific workstreams in different areas, and for expert groups to address highly focused and relevant matters. In the SA context, most, if not all, of these areas already exist with well-established working groups/societies/non-profit organisations. Table 5 lists self-regulatory professional bodies in SA. The National Department of Health must lead this process and involve other stakeholders, such as the Health Professions Council of SA and the SA National Accreditation System.

Terminology

A common terminology enables technology, facilitating communication between researchers, legislators, regulators and practitioners. For a term to have meaning, it must be unambiguous. Therefore, when Acts and their regulations are revised or constructed, care should be taken to define and use terminology appropriate for those statutes' values, but permissive enough not to stifle progress and development. It is also essential to use the same terminology across various laws and their associated guidelines to avoid ambiguity in interpretation.[29] While there is a common law principle that 'a statute is always speaking,' its interpretation becomes problematic if the meanings of defined terms are inconsistent or ambiguous, or have fundamentally changed over time.[30] There is no internationally harmonised terminology or classification system for advanced cell-based products. However, a project is underway at the Institute for Cellular and Molecular Medicine at the University of Pretoria, in co-operation with the South African Stem Cell Transplantation Society, to develop a basis for shared terminology in our country.

Conclusion

With the sequencing of the human genome and the ability to modify stem and somatic cells *ex vivo* and *in vitro* came the realisation that a wide range of disorders can now be treated by identifying and utilising cellular and molecular detail regarding disease pathogenesis at the highest resolution possible. This has resulted in the rapid emergence of new and disruptive medicines that have outstripped existing regulatory frameworks. Several jurisdictions have responded by enacting legislation that ensures patient safety, therapeutic efficacy

and adequate quality control. Despite the high burden of disease and the exciting opportunities to apply novel therapies to treat these diseases at scale, SA has yet to respond. The authors propose that this can be addressed rapidly by creating a much-needed regulatory framework in a two-step process that balances the need for guidance with the promotion of technological advances to improve the quality of life of our patients.

Data availability. N/a.

Declaration. This article was written to partly fulfil the requirements of IMV's MSc in Medical Immunology.

Acknowledgements. None.

Author contributions. MSP and IMV co-conceptualised the overarching thematic and MSP provided the first draft. IMV developed and extended the thematic, and researched and wrote the detailed manuscript. MSP reviewed and edited the manuscript throughout.

Funding. This work was funded by the South African Medical Research Council (Extramural Unit for Stem Cell Research and Therapy) and the University of Pretoria through the Institute for Cellular and Molecular Medicine.

Conflicts of interest. None.

1. Constitution of the Republic of South Africa, 1996.
2. South Africa. Medicines and Related Substances Act No. 101 of 1965.
3. South Africa. Medicines and Related Substances Amendment Act No. 14 of 2015.
4. South Africa. National Health Act No. 61 of 2003.
5. South Africa. Genetically Modified Organisms Act No. 15 of 1997.
6. South Africa. Medicines and Related Substances Act, 1965. General Regulations. Government Gazette No. 41064, 2017.
7. National Department of Agriculture Forestry and Fisheries, South Africa. Genetically Modified Organisms Act of 1997. Regulations. Government Gazette 32966, 2010 as amended.
8. South Africa. National Health Act No. 61 of 2003. Regulations Relating to the Use of Human Biological Material. Government Gazette No. 35099, 2012.
9. South Africa. National Health Act No. 61 of 2003. Regulations Relating to Blood and Blood Products. Government Gazette No. 35099, 2012.
10. South Africa. National Health Act No. 61 of 2003. Regulations Regarding the General Control of Human Bodies, Tissue, Blood Products and Gametes. Government Gazette No. 35099, 2012.
11. South Africa. National Health Act No. 61 of 2003. Regulations Relating to the Import and Export of Human Tissue, Blood, Blood Products, Cultured Cells, Stem Cells, Embryos, Foetal Tissue, Zygotes and Gametes. Government Gazette No. 35099, 2012.
12. South Africa. National Health Act No. 61 of 2003. Regulations Relating to Tissue Banks. Government Gazette No. 35099, 2012.
13. South Africa. National Health Act No. 61 of 2003. Regulations Relating to Stem Cell Banks. Government Gazette No. 35099, 2012.
14. European Union.Regulation (EC) No 726/2004 on laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. 31 March 2004. Directive 2001/83/EC on the community code relating to medicinal products for human use. 6 November 2001.
15. European Union. Regulation (EC) No 1394/2007 on advanced therapy medicinal products. 30 December 2008.
16. United States of America. Federal Food, Drug, and Cosmetic Act as Amended through PL 117-328. Enacted December 29, 2022.
17. United States of America. Section 351 of the Public Health Services Act. Regulation of biological products, (1 July 1944, 1944).
18. United States of America. Section 361 of the Public Health Services Act. Regulation to control communicable diseases, (1944).
19. United States of America. 21 CFR Part 600 - Biological Products. General. 59 FR 54042 (1994).
20. United States of America. 21 CFR Part 1271 - Human cells, tissues, and cellular and tissue-based products as amended. 21 CFR Part 1271 (2023).
21. Australia. Therapeutic Goods Act No. 21 of 1990. Compilation No. 85, 1 July 2024. Therapeutic Goods Amendment (2009 Measures No. 3) Act No. 54, 2010, Pub L No. C2010A00054. 31 May 2010.
22. European Union. Regulation (EU) No 2024/1938 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC. 13 June 2024.
23. Japan. The Regenerative Medicine Promotion Act No.13 of 2013.
24. Japan. Act on Ensuring the Safety of Regenerative Medicine. Act No. 85 of 2013.
25. Japan. Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Device. Act No. 145 of August 10, 1960.
26. USA. Food and Drug Administration Modernisation Act of 1997. Public Law 105-115. I l l STAT. 2296. 21 November 1997.
27. USA. The 21st Century Cures Act. 13 December 2016.
28. USA. Food and Drug Omnibus Reform Act of 2022. Public Law 117–328. 29 December 2022.
29. South Africa. Parliamentary Committee on Health. Submission by the SA Medical Association: Concerns about Section 46 and Chapter 8 regulations. 2013. https://pmg.org.za/committee-meeting/15989/ (accessed 31 August 2024).
30. Royal College of Nursing of the United Kingdom v Department of Health and Social Security [1981] UKHL J0205-3AC 800 p 822 B-E: (1981).

Received 12 September 2024; accepted 27 September 2024.