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Regenerative medicines: A new regulatory paradigm for South Africa

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ABSTRACT

Clinicians are increasingly using regenerative medicines to repair, replace, regenerate or rejuvenate lost, damaged or diseased genes, cells, tissues or organs. In South Africa, access to these novel gene therapies and cell and tissue-based products is limited. The human leukocyte antigen (HLA) diversity and a paucity of suitable HLA-identical unrelated donors, results in limited access to haematopoietic stem and progenitor cell transplantation (HSPCT). Cell-based products could increase this access. Genetic diversity can also manifest in local or region-specific rare congenital disorders, and *in vivo* gene therapies hold the promise of developing treatments and cures for these debilitating disorders. South Africa has a disproportionate mortality rate due to non-natural causes, with many surviving with permanent injuries and disabilities. Tissue-engineered cell-based products have the potential to restore many of those affected and improve quality of life and productivity. These factors create an urgency for South Africa to develop regenerative medicines to address the country's unique needs and to provide access to these new and innovative treatment modalities. Achieving this objective requires a well-coordinated effort by multiple stakeholders and role players. A critical component of a regenerative medicine ecosystem is establishing an enabling regulatory framework for these new classes of medicines.

Here we provide a brief profile of South Africa, including its genetic diversity, economy, the impact of the burden of disease, health policy and the healthcare system. We address the regulation of medicines, how the existing framework can accommodate regenerative medicines, and the steps needed to establish a future regulatory framework.

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1. South Africa: Short profile

1.1. Genetic diversity

South Africa (SA) has a genetically diverse population of more than 60 million people, comprising approximately 49 million persons of African ethnolinguistic groups, 5 million of mixed ancestries, 1.5 million people of Indian and Asian ancestry, and 4.6 million persons of European descent [1]. The African and mixed-ancestry population groups contain ethnically distinct subpopulations [2]. This heterogeneity is reflected in human leukocyte antigen (HLA) diversity among these multiple population groups. HLA diversity, combined with a low representation of African and mixed-ancestry groups in donor registries together with the absence of public cord blood banks [3], results in a paucity of HLA-matched unrelated donors for patients in need of haematopoietic stem and progenitor cell transplantation (HSPCT). Recent work by Du Toit et al. has demonstrated that haploidentical HSPCT with post-transplantation cyclophosphamide (PT-Cy) results in favourable outcomes in the South African population which expands the donor pool to include haploidentical related donors [4]. This is one measure that can be implemented to overcome the paucity of matched donors and provide more patients access to HSPCT.

Genetic diversity can also manifest as higher birth prevalence of rare congenital disorders specific to regions and localities. Sickle cell disease (SCD) is a well-documented genetic blood disorder that affects an estimated 4,4 million people of African descent worldwide, with 80% located in sub-Sahara Africa (SSA) [5]. There are also several other lesser-known rare congenital disorders that may severely impact local populations. Examples include genetic mutations that may lead to deafness or blindness in some SSA populations [6] and Mseleni joint disease (MJD), a rare and crippling chondrodysplasia that severely affects the hip and other joints. MJD is reported mainly in the Maputuland region in northern Kwazulu Natal. While the aetiology of the disease is still unknown, a genetic or origin cannot be excluded [7].

1.2. Economy and employment

The World Bank classifies SA as an upper-middle-income country based on its average per capita gross domestic product (GDP) [8], and the United Nations Development Programme (UNDP) rates SA as a country with a high Human Development Index (HDI) [9]. Both GDP and HDI are based on averages, which effectively obscure inequalities within a country. An alternative measure is the Gini index, which measures the inequality of income or wealth distribution across a population [10]. A Gini score of zero represents total equality and a score of one is absolute inequality. With a Gini index of 0.63, South Africa is rated as the most unequal country in the world [11]. 0.1% of the adult population or 35 000 individuals hold more than a third of the wealth, and more than half of the population is in debt [12]. It should be noted, however, when taxation and the disbursement of social grants are factored in, the Gini score decreases to 0.47 [13].

A major contributor to this inequality is unemployment. The official unemployment rate was 34.9% in Q3 of 2021 and when discouraged work-seekers was included, the total unemployment rate was 46.6% during the same period. The economically active population was only 14.3 million people during the same period [14]. Unemployment impacts the country in multiple ways. It limits the tax base to 6.3 million people, with a quarter of those contributing 80% of the country's personal tax [15]. The high proportion of unemployment increases the burden of social grants, detracting from much-needed investment in education, health and other important projects.

1.3. Burden of disease

SA faces a quadruple disease burden of poor maternal, newborn and child health, communicable and non-communicable diseases (NCDs) and disproportionally high mortality and morbidity due to unnatural deaths. In 2018, communicable diseases, maternal and perinatal causes and malnutrition contributed 28.8% of deaths. NCDs, including cancer, diabetes, heart disease and asthma account for almost 60% of deaths [16]. These parallel burdens of persisting and emerging infectious diseases together with rising NCDs seen in SA and other low and middle-income countries (LMIC) is very different to the classical epidemiological transition experienced in high-income countries – where infectious diseases were largely eradicated before chronic conditions took precedence as life expectancy at birth increased [17] SA also has one of the highest mortality rates for non-natural causes (accidents, homicide and suicide) which exceeds tuberculosis and HIV/AIDS mortality combined and is >40% in the 15 to 35-year age group and 12% overall. These numbers indicate life-years lost due to premature death but exclude disability and so do not quantify the complete burden of disease. There are an estimated 10 to 50 survivors for every trauma-related death and half of these survivors will survive with permanent disabilities [18]. In SA, as in most LMICs, a lack of access to rehabilitation services leads to an increase in disability-adjusted life-years (DALYs) [19].

DALYs measure life-years lived with a disability combined with years of life lost due to premature death from a specific disease and intervention. The DALY is a composite measure of health status. Together with Quality Adjusted Life Years (QALYs), they are commonly used in cost-utility analyses in economic evaluation. These evaluation studies are a key component in Health Technology Assessments (HTA), used in decision making and the allocation of limited health resources. Prior to 2016, the World Health Organization (WHO) benchmark for LMICs was between one and three times the gross domestic product (GDP) per capita per DALY averted. However, this approach was not based on a scientifically

justified rationale and was discontinued. Working with 2015 mortality and morbidity data, Edoka and Stacey [20] proposed a cost-effectiveness threshold (CET) for SA of ZAR 38 500 (US$ 2500) per DALY averted, or approximately 53% of GDP per capita in 2015. The UK National Health Service (NHS) and the National Institute for Health and Care Excellence (NICE) use QALYs as a benchmark. The NICE independent committees use a threshold of between £20 000 and £30 000 per QALY for recommending treatments [21]. Some health economists argue, however, that an amount of £13 000 would be more appropriate [22]. Unit costs and Purchasing Power Parity (PPP) vary between countries, making it difficult to directly transfer costs from one country to another.

1.4. Health policy

The Constitution of the Republic of South Africa grants all South Africans the right to access to health and social care services, and the state must "take reasonable legislative and other measures to achieve these rights" within its available resources. (s. 27 (1)(a)) [23].

SA has a dual healthcare system of public and private care. Approximately nine million members (16% of the population) have private health insurance [24,25], with the remaining, approximately 50 million individuals, relying on public healthcare [26,27].

An NHI framework and funding mechanism are being developed to achieve universal health care [28], but severely limited human and financial resources, further exacerbated by the COVID-19 pandemic, are hampering its implementation. NHI will be implemented in a phased approach while preventing and treating communicable and NCDs through packages of care, investing in health infrastructure and aligning national health research with these priorities [29].

2. Medicine regulation in South Africa

SA has a well-established medicines regulatory framework. The original *Drugs Control Act* was promulgated in 1966 "to provide for the registration of drugs intended for human use and to establish a Drugs Control Council" [30]. Formal drug regulation began in 1968, and the Act was then amended several times. In its current form, it is known as the *Medicines and Related Substances Act,1965* (MRS Act) [31] and is supported by General Regulations (MRS Regulations) issued by the Minister of Health [31]. The Drug Control Council later evolved into the Medicines Control Council (MCC) and, most recently, into the South African Health Products Regulatory Authority (SAHPRA).

2.1. SAHPRA

SAHPRA's objectives " … are to provide for the monitoring, evaluation, regulation, investigation, inspection, registration and control of medicines, scheduled substances, clinical trials and medical devices, IVDs and related matters in the public interest" (s.2A).

The Authority has Recognised Regulatory Agency (RRA) agreements with the FDA, EMA (for both centralised and decentralised marketing authorisation procedures), the MHLW, TGA, Health Canada, Swissmedic and the UK Medicines and Health Products Regulatory Agency (MHRA) and can also rely on WHO prequalification and Zazibona regional collaborative procedures.

Since 2007, SAHPRA has been a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and can rely on other members' inspections of manufacturing sites [33]. As a PIC/S member, SAHPRA has adopted the PIC/S guides to Good Manufacturing Practices (GMP) as the South African GMP Guidelines [34] and amended Annex 16 to provide for SA-specific requirements for manufacturing organisations and their personnel.

Table 1 lists important legal and regulatory instruments that apply to the regulation of medicines in SA and other instruments that would impact the regulation of AT or RMs.

2.2. Medicines registration

One of SAHPRA's responsibilities is the registration of medicines, and for this purpose they use the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) harmonised Common Technical Document (CTD) [44]. Since 2017, the electronic CTD has been the preferred application format. This permits SAHPRA to use full, abridged and verified reviews or to directly rely on the outcomes of RRA reviews, such as the EMA summary of product characteristics (SmPC), to register new chemical entities (NCEs).

2.3. Prohibition of the sale of medicines subject to registration

Section 14(1) of the MRS Act prohibits the sale of medicines that require registration if they are not registered. The SAHPRA executive may determine by proclamation in the Government Gazette which medicines, categories or classes of medicine are subject to registration. The regulation of regenerative medicines (RMs) has not been gazetted, leaving a regulatory vacuum [45,46].

Some medicines are exempt from registration: 1) Medicines compounded by a pharmacist, or another licenced person, under conditions specified in section 14(4)) of the MRS Act and MRS regulation 3, are excluded from registration; 2) Similarly, section 21 of the Act permits SAHPRA to authorise the sale of a specified quantity of an unregistered medicine to a specified person or institution and for a specified period, enabling treatment for many (rare) diseases where there is no other treatment option. This is comparable to the EU compassionate use provision of Regulation (EC) No 726/2004 article 83 [47] and article 5 of Directive 2003/83/EC [48]. These products are in the EU often referred to as "specials"; MRS Regulation 29 provides the specific requirements for such an authorisation. 3) MRS Regulation 30 regulates the conduct of clinical trials per Good Clinical Practice (GCP) [49] and the national research ethics guidelines [50]. Once SAHPRA approves a clinical trial protocol, this allows the importation of unregistered investigational products (IP).

3. Regenerative medicine and regenerative medicines

Regenerative medicine was defined in 2008 as the "process of replacing, engineering or regenerating human or animal cells, tissues or organs to restore or establish normal function" [51]. The Center for Regenerative Medicine at Mayo Clinic defines Regenerative medicine as " … focused on developing and applying new treatments to heal tissues and organs and restore function lost due to aging [sic], disease, damage or defects" [52]. We differentiate between regenerative medicine as a multidisciplinary field of medicine and RMs as a diverse range of manufactured medicinal products. These products include *in vivo* gene therapies (GTs) and cell-based products (CBPs). A CBP is any manufactured medicinal product that contains or consists of substantially manipulated live human (or animal) cells or tissues, alone or in combination with other non-cellular substances, materials, components or devices, and includes gene-modified (GM) CBPs.

3.1. Regulation of RM globally

Several regulatory jurisdictions, including the United States,

Table 1
Legal instruments that could impact the regulation of regenerative medicines in South Africa.

Title	Description	Date
Constitution of the Republic of South Africa [23]	This Constitution is the supreme law of the Republic; law or conduct inconsistent with it is invalid, and its obligations must be fulfilled.	August 23, 2013 (17th amendment)
Medicines and Related Substances Act, 1965 (Act No. 101 of 1965) [31]	Establishes the South African Health Products Regulatory Authority. Provides for the regulation of medicines (MRS Act)	June 1, 2017
General Regulations to the Medicines and Related Substances Act of 1965 [32]	Regulations to the Medicines and Related Substances Act, 1965. (MRS Regulations)	August 25, 2017
Genetically Modified Organisms Act, 2007 (Act 15 of 1997) [35]	Provide for measures to promote the responsible development, production, use and application of genetically modified organisms (GMO Act)	April 17, 2007
National Health Act, 2003 (Act No 61of 2003) [36]	Provides a framework for a structured health system in South Africa and takes into account the obligations imposed by the Constitution (NH Act)	September 2, 2013
Government Notice R. 175 [37]	Regulations relating to Artificial Fertilisation of Persons (R. 175)	March 2, 2012
Government Notice R. 177 [38]	Regulations regarding Human Biological Materials (R. 177)	March 2, 2012
Government Notice R. 179 [39]	Regulations relating to Blood and Blood Products (R. 179)	March 2, 2012
Government Notice R. 180 [40]	Regulations regarding the General Control of Human Bodies, Tissue, Blood, Blood Products and Gametes (March 2, 2012) and amended by Government Notice 392 in Government Gazette 40816 (R. 180)	April 26, 2017
Government Notice R. 181 [41]	Regulations relating to the Import and Export of Human Tissue, Blood, Blood Products, Cultured Cells, Stem Cells, Embryos, Foetal Tissue, Zygotes and Gametes (R. 181)	March 2, 2012
Government Notice R. 182 [42]	Regulations on Tissue Banks (R. 182)	March 2, 2012
Government Notice R. 183 [43]	Regulations on Stem Cell Banks (R. 183)	March 2, 2012

European Union, Japan and Australia have recognised that these new therapeutic modalities meet the definition of medicines [drugs, medicinal products, pharmaceuticals] since they are manufactured products containing an active pharmaceutical ingredient. They may be used to diagnose, prevent, treat, mitigate or cure diseases, disorders or injuries through the therapeutic activity of the active ingredient.

As medicines, they should be assured to be safe, effective and of good quality, and thus fall under the statutory authority of national or regional medicines and health product regulatory authorities. However, it was also recognised that the established regulatory frameworks designed for small and biological molecule-based medicines do not address these regenerative products' novelty, complexity and technical specificity. *Lex specialis* or amendments to existing legal and regulatory instruments were required to accommodate these new classes of medicines and to protect the public interest.

Globally, there is no harmonised definition, terminology, or regulatory framework for regenerative medicines. A variety of approaches have been taken around the world, including:

In the US, minimally manipulated human cell and tissue-based products (HCT/Ps) are solely regulated under 21 CFR 1271 and section 361 of the Public Health Services (PHS) Act, while others are regulated as biologicals, drugs and regenerative medicine therapies (RMTs) under section 351 of the PHS Act, the Food Drug and Cosmetic (FD&C) Act and FDA regulation 21 CFR 1271 [53,54].

In the European Union (EU), advanced therapy medicinal products (ATMPs) include gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (CTMPs), tissue-engineered products (TEPs) and combination ATMPs. Industrially manufactured products for EU inter-Member State commerce are regulated by the European Medicines Agency (EMA) Committee for Advanced Therapies (CAT), and non-routine custom prepared products for individual patients in hospitals may be regulated by national competent authorities (NCAs) in terms of Directive 2001/83/EC article 3(7), the so-called "hospital exemption" (HE) [48].

Japan defines a "regenerative medicine product" in article 2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices as:

> "(i) … items intended for use in human or animal healthcare which are obtained after culturing or other processes using human or animal cells: (a) reconstruction, repairing or formation of the structure or function of the bodies of humans or animals; (b) treatment or prevention of disease in humans or animals; (ii) items intended for use in the treatment of disease in humans or animals which are introduced into cells of humans or animals and contain genes to be expressed in their bodies." [55].

They further classify RMs on a risk basis into three classes with appropriate levels of control. The country has a dual system whereby RMs prepared for individual patients in hospitals and clinics are directly regulated by the Ministry of Health, Labour and Welfare (MHLW). In contrast, commercial RMs are regulated by the Pharmaceutical and Medical Devices Agency (PMDA).

In Australia, article 32A of the Therapeutic Goods (TG) Act defines a biological as:

> " … a thing that either (i) comprises, contains or is derived from human cells or human tissues; or is specified [to be a biological] …; and is represented in any way to be, or is, whether because of the way in which it is presented or for any other reason, likely to be taken to be:
>
> (i) for use in the treatment or prevention of a disease, ailment, defect or injury affecting persons; or
> (ii) for use in making a medical diagnosis of the condition of a person; or
> (iii) for use in influencing, inhibiting or modifying a physiological process in persons; or
> (iv) for use in testing the susceptibility of persons to a disease or ailment; or
> (v) for use in the replacement or modification of parts of the anatomy in persons." [56].

Biologicals include *ex vivo* gene-modified cell therapies, but *in vivo* gene therapies are regulated as prescription medicines. Like in Japan, biologicals in Australia are classified into four risk-based classes with appropriate levels of regulation. Gene therapies, gene-modified cell therapies, Class 3 and 4 biologicals and biologicals combined with devices are classified as advanced therapies (ATs).

SA, like other LMIC countries, has not developed an RM-specific regulatory framework.

4. Commercial regenerative medicines regulation in South Africa

Advanced therapies are not yet defined in the MRS Act and its regulations. However, the Act does define "medicine" as:

> " … any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in (i) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in humans; or (ii) restoring, correcting or modifying any somatic or psychic (sic) or organic function in humans … " [31].

While this definition was formulated before the emergence of RM therapies and may be considered outdated, it is sufficiently broad in scope to include advanced regenerative therapies, placing the onus on SAHPRA to regulate these products in the public interest. In theory, SAHPRA can register commercial RM products that are already authorised by other RRAs using recognition procedures, through Section 21 permission or for clinical trial use.

4.1. *In vivo gene therapies*

Internationally, two gene therapies have in recent years been approved; Zolgensma is used to treat spinal muscular atrophy by delivering a functional copy of the human survival motor neuron gene (SMN1) to patients *in vivo*. Luxturna is used to treat patients with inherited retinal dystrophy by driving the expression of normal human retinal pigment epithelium 65 kDa protein [57,58].

These *in vivo* gene therapies could be registered in SA using recognition pathways, Section 21 compassionate use permission, clinical trial investigational product authorisation or existing biological medicines regulations. There are however additional regulatory challenges related to genetically modified organisms (GMO) that will have to be overcome. As in the EU, Japan and Australia, GTs and G-M CPTs products are GMOs in SA.

4.1.1. *Genetically Modified Organisms Act No. 15 of 1997*

The GMO Council in the Department of Agriculture administers the *Genetically Modified Organisms Act* No. 15 of 1997 (GMO Act) [35]. In the GMO Act, gene therapy is defined as: "a technique for delivering functional genes (to replace aberrant ones) into living cells utilizing a genetically modified vector or by physical means to genetically alter the living cell".

The GMO Act applies to the use of gene therapy (s.2(1)(c)), but does not apply to techniques involving human gene therapy (s.2(2)(a)).

The GMO Council also reviews vaccines, including those for COVID-19, used in clinical trials, and once approved for clinical trial use they are generally not reviewed again for registration. There is to date no precedent for registering a GT product that is already registered by another RRA or allowing the importation of a GT or G-M CBP under Section 21. Imported investigational GT or G-M CBP would be subject to approval by the GMO Council, raising specific coordination and timing challenges since both the GMO council and SAHPRA clinical trial committees meet only six times a year.

4.2. *Cell-based and gene-modified cell-based therapies*

Kymriah, Yescarta, Tecartus, Abecma and Breyanzi are T-cells that have been *ex vivo* genetically modified to express a chimeric antigen receptor directed against CD19 or B-cell maturation antigen (BCMA) tumour cell surface proteins and that are administered in an autologous manner. Kymriah (tisagenlecleucel, Novartis) is used to treat relapsed/refractory diffuse large B-cell lymphoma at US$ 370 000 for a single dose. Leukapheresis and a two-month follow-up increase the cost to an estimated US$ 434 000–510 000 per treatment [59].

In theory, SAHPRA could use recognition procedures to register GM CBPs, or Section 21 or clinical trial procedures to authorise the importation of these products. For GM CBPs, the GMO regulations and regulations related to the use of human biological materials would also apply.

4.2.1. *National Health Act, No 61 of 2003 (Chapter 8)*

The *Control of Use of Blood, Blood Products, Tissue and Gametes in Humans* is legislated by Chapter 8 of the National Health Act, No. 61 of 2003 (NH Act) and several regulations have been promulgated to address various aspects of this chapter. Unfortunately, these regulations lack alignment, resulting in fragmentation and confusion. The NHA Act predates the advances made during the past two decades in the RM field and is focused on hESCs and donated blood, haematopoietic stem cells and tissue for transplantation. It does not address the use of somatic cells and tissue as starting material for the manufacture of cell- and tissue-based medicinal products, nor the establishment of cell lines. The various regulations are listed in Table 1 above.

Regulation R. 181 relates to the export and import of HBMs, including cultured cells. No person may import or export HBM without a permit (R. 181 s. 2). The authorised institution must keep records for five years and submit reports every six months to the Director-General of Health. (R. 181 s.7) While the import or export of HBM is an established procedure, there is no precedent for the export and reimportation of the same cells or human GM cells.

R. 179 s.9 deals with mandatory testing of donated blood and blood products for transmissible diseases and R. 183 s.2 with the testing of stem cells. In both cases, the testing of autologous cells is not required.

In the case of a registered autologous CBP such as MACI (matrix applied characterised autologous cultured chondrocytes) to repair cartilage defects of the knee, the same regulations would apply.

4.3. *Summary: commercial regenerative medicines*

SAHPRA can use recognition pathways to evaluate and register industrially manufactured commercial gene- and cell-based therapies in SA. Several additional regulatory and administrative challenges must also be addressed, but the biggest challenge to access however is treatment cost.

5. Custom prepared regenerative medicine products

The international pharmaceutical industry is profit-driven and focuses its research and development activities on diseases and markets that can deliver substantial returns on investment. While internationally marketed commercial RMs may address some unmet medical needs in SA, the country is, from a pharmaceutical industry profit perspective, an unattractive market, and logistics and regulatory challenges further contribute to complexity.

Internationally, many CBPs are custom prepared in cell-processing facilities and academic centres to provide individual patients with much-needed therapies. In the EU, this is permitted under "hospital exemption" (HE). The HE places the responsibility on NCAs to ensure that these custom prepared products are manufactured to specific quality standards and that national traceability and pharmacovigilance is done to the same standards as required in the EU. Several criticisms are levelled at the exemption; most notable is the different interpretations of NCAs and that, in several countries, the use of products under the HE falls outside of clinical trial regulations [60].

Table 2
List of initial guidelines for the regulation of gene therapies and cell-based products.

Agency	Document Number	Guideline
PIC/S	(Annex 2A) [63]	PIC/S GMP standards on the manufacture of advanced therapy medicinal products for human use
EMA	EMEA/CHMP/410869/2006 [64]	Guideline on Human Cell-based Medicinal Products
EMA	EMA/CAT/GTWP/671639/2008 [65]	Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells
EMA	EMA/CAT/852602/2018 [66]	Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials
EMA	EMEA/CHMP/SWP/28367/07 [67]	Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products
ICH	ICH Q5D [68]	Derivation and characterisation of cell substrates used for the production of biotechnological/biological products
Ph. Eur	Ph. Eur 5.2.12 [69]	Raw materials of biological origin for the production of cell-based and gene therapy medicinal products
FDA	21CFR 1271 Subpart D [70]	Current Good Tissue Practices
USP	USP 1043 [71]	Ancillary Materials for Cell, Gene and Tissue-Engineered Products
EMA	EMA/CHMP/BWP/271475/2006 [72]	Guideline on potency testing of cell-based immunotherapy medicinal products for the treatment of cancer
ICH	Topic Q5B [73]	Note for guidance on the quality of biotechnological products: analysis of the expression construct in cell lines used for the production of r-DNA derived protein products

A modified HE approach may offer an alternative route to RM access for South African patients. This will require a focused and phased approach on priority conditions together with the development or in-licensing of platform technologies to address both costs and health benefits/outcomes.

Hendricks et al. have recently proposed the creation of a South African Cell and Gene Therapy Society as a dedicated platform for stakeholders. Such a platform would allow for all relevant stakeholders from academic and private institutions to collaborate towards the common goal of bringing cell and gene therapies to South Africa in a coordinated effort. As critical steps towards equitable access to cell and gene therapies in SA, they propose, in close liaison with Government and supported by funding, the establishment of rare disease registries to track patients; the building of human, research and manufacturing capacity; and the development of a centralised clinical facility [61]. These initiatives must be underpinned by an appropriate legal and regulatory framework to support the research, development, authorisation and access to RMs in SA [62]. We now briefly discuss how SAHPRA can facilitate the regulation of custom prepared CBT products, including G-M CBTs.

5.1. A way forward: Recommendations

Section 14(2) of the MRS Act allows the SAHPRA executive to determine by proclamation in the Government Gazette which medicines, categories or classes of medicine are subject to registration. This declaration triggers a process involving consultation with stakeholders, drafting new regulations or amendments of existing regulations, and possible amendments to Acts of Parliament.

There is an initial need to define the related terms, classification of RMs, and set clear authorisation requirements before these products can be administered to human patients. Potential steps may include:

- The SAHPRA CEO declares the intention to regulate RMs in the Government Gazette and the creation of a new category of medicines (as in the EU) or a new class of health products (as in Japan and Australia).
- Development and dissemination of an implementation roadmap including definitions and draft regulations.
- Undertaking a stakeholder participation process, including the proposed South African Cell and Gene Therapy Society or a similar body.
- Development of standards, certification and licensing procedures for cell-processing facilities.
- Establishment of an authorisation procedure for custom prepared advanced therapies.
- Publication of draft guidelines related to these products' quality, safety, and efficacy requirements for public input. At this early stage, SAHPRA could initially rely on the guideline documents included in Table 2.
- Propose amendments to MRS, HN, GMO and alignment to other Acts
- Gazette the final regulations.

6. Conclusion

Regenerative gene, cell and tissue-based medicines are increasingly offering new treatment modalities for previously untreatable and incurable diseases and for the restoration of function following traumatic injuries. While commercial RM and AT medicinal products are authorised in high-income countries, they are prohibitively expensive, which will prevent similar access in LMICs. It is necessary for SA to develop a strategy to improve access to these products, including a regulatory framework for custom prepared non-commercial ATs that meet the appropriate quality, safety, and efficacy standards.

Declaration

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Author contributions

IMV and CLH conceptualised, researched, and wrote the original draft. MSP and HL reviewed and edited the manuscript throughout. All authors contributed equally to the preparation of this manuscript.

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Declaration of competing interest

None.

References

[1] Statistics South Africa. Mid-year population Estimates 2021. [Internet] Pretoria 19 July 2021 (P0302): p.15 Mid-Year Population Estimates 2021. [cited 3 October 2021] Available from: http://www.statssa.gov.za/.

[2] M. Daya, L. Van der Merwe, U. Galal, et al., A panel of ancestry informative markers for the complex five-way admixed South African Coloured population, PLoS One 8 (12) (2013), e82224.

[3] I.M. Viljoen, C.L. Hendricks, J. Mellet, M.S. Pepper, Perspectives on establishing a public cord blood inventory in South Africa, Cytotherapy 23 (6) (2021) 548–557, https://doi.org/10.1016/j.jcyt.2021.02.116.

[4] J.R. Du Toit, A. Mcdonald, D. Brittain, M. Cass, J. Thomson Oosthuizen, et al., Is Haploidentical Hematopoietic Cell Transplantation Using Post-Transplantation Cyclophosphamide Feasible in Sub-saharan Africa? Transplantation and Cellular Therapy, 2021 https://doi.org/10.1016/j.jtct.2021.08.018. ISSN 2666-6367.

[5] Global Burden of Disease Study 2013 Collaborators, Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013, Lancet (London, England) 386 (9995) (2015) 743–800, https://doi.org/10.1016/S0140-6736(15)60692-4.

[6] J.R. Rudman, R.I. Kabahuma, S.E. Bressler, Y. Feng, S.H. Blanton, D. Yan, et al., The genetic basis of deafness in populations of African descent [Internet]. Elsevier BV, J. Genet. Genom. 44 (6) (2017 Jun) 285–294, https://doi.org/10.1016/j.jgg.2017.03.008. Available from:.

[7] E.S. Dinkele, R. Ballo, V. Fredlund, R. Ramesar, V. Gibbon, Mseleni joint disease: an endemic arthritis of unknown cause [Internet]. Elsevier BV, Lancet Rheumatol. 2 (1) (2020 Jan) e8–e9, https://doi.org/10.1016/s2665-9913(19)30104-3. Available from:.

[8] The World Bank: Country Data [Internet] [ ]cited 12 October 2021] Available from https://data.worldbank.org/country/ZA.

[9] UNDP: Human Development Report 2020: South Africa [Internet] Available from http://hdr.undp.org/sites/default/files/Country-Profiles/ZAF.pdf [cited 12 October 2021] p. 2.

[10] C. Gini, On the Measure of Concentration with Special Reference to Income and Statistics, vol. 208, Colorado College Publication, General Series No, 1936, pp. 73–79.

[11] World Population Review, Gini Coefficient by Country 2020 [Internet], World Population Review, 2021 [cited 12 October 2021]. pp. 1–8.

[12] A. Chatterjee, L. Czajka, A. Gethin, Estimating the Distribution of Household Wealth in South Africa, WIDER Working Paper [Internet], UNU-WIDER, 2020, https://doi.org/10.35188/unu-wider/2020/802-3. Available from:.

[13] M. Schüssler, The Gini Is Still in the Bottle [Internet], Money Web, 16 July 2014 [cited 28 January 2022] Available from: https://www.moneyweb.co.za/archive/the-gini-is-still-in-the-bottle/.

[14] Statistics South Africa. Quarterly Labour Force Survey (QLFS) Q3:2021. [Internet] Pretoria 30 November 2021 Media Release. [cited 3 February 2022] Available from: http://www.statssa.gov.za/?p=14957.

[15] PwC: Budget Highlights 2021: [Internet] [cited 3 February 2022] Available from: https://www.pwc.co.za/en/publications/budget.html.

[16] Statistics South Africa. P0309.3 - mortality and causes of death in South Africa: Findings from death notification, 2018 [Internet] [cited 3 February 2022] Available from: http://www.statssa.gov.za/publications/P03093/P030932018.pdf.

[17] H.L. Malherbe, C. Aldous, A. Christianson, Need for services for the care and prevention of congenital disorders in South Africa as the country's epidemiological transition evolves, S. Afr. Med. J. 105 (3) (2015) 186–188.

[18] T.C. Hardcastle, G. Oosthuizen, D. Clarke, E. Lutge, Trauma, a preventable burden of disease in South Africa: review of the evidence, with a focus on KwaZulu-Natal, SAHR (2016) 179–189.

[19] R.A. Gosselin, D.A. Spiegel, R. Coughlin, L.G. Zirkle, Injuries: the neglected burden in developing countries, Bull. World Health Organ. 87 (2009), 246–246a. [Internet] [cited 3 February 2022] Available from: https://apps.who.int/iris/handle/10665/270409?locale-attribute=es&.

[20] I.P. Edoka, N.K. Stacey, Estimating a cost-effectiveness threshold for health care decision-making in South Africa, Health Pol. Plann. 35 (5) (2020 Jun 1) 546–555, https://doi.org/10.1093/heapol/czz152.

[21] NICE Website: Sir Andrew Dillon; Carrying NICE over the threshold, 19 February 2015 [Internet] [cited 3 February 2022] Available from: https://www.nice.org.uk/news/blog/carrying-nice-over-the-threshold.

[22] K. Claxton, S. Martin, M. Soares, N. Rice, E. Spackman, S. Hinde, et al., Methods for the estimation of the NICE cost effectiveness threshold, Health Technol. Assess. 19 (14) (2015), https://doi.org/10.3310/hta19140.

[23] South African Parliament, Constitution of the Republic of South Africa, South African Government Gazette, 2006, p. 17678. Notice No. 2083 [Internet] [cited 3 February 2022] Available from: http://www.lawsofsouthafrica.up.ac.za.

[24] Xe Live Exchange Rates [Internet] [cited 8 February 2022] Website: https://www.xe.com/currencyconverter/.

[25] Council for medical Schemes: Annual report 2019/20, ISBN: 978-0-621-48475-5 [Internet] [cited 3 October 2021] Available from: https://www.medicalschemes.co.za/publications/#2009-3506-wpfd-2019-20-annual-report.

[26] National Treasury: Budget 2021/22 Budget Highlights [Internet] [cited 3 February 2022] Available from: http://www.treasury.gov.za/documents/National%20Budget/2021/sars/Budget%202021%20Highlights.pdf.

[27] National Treasury: Budget 2021/22 Estimates of national Expenditure [Internet] [cited 3 February 2022] Available from: http://www.treasury.gov.za/documents/National%20Budget/2021/ene/FullENE.pdf.

[28] South Africa Department of Health: National Health Insurance Bill as Introduced to the National Assembly Published in Government Gazette No. 42598 of 26 July 2019.

[29] South Africa: National Department of Health, National Health Research Committee (NHRC), (2021), National health research strategy: research priorities for SA 2021-2024. [Internet] [cited 10 October 2021] Available from: https://health.gov.za/strategic-documents/.

[30] Senate and House of Assembly of the Republic of South Africa: Drugs Control Act No. 101 of 1965. Government Gazette 1171 dated 7 July 1965.

[31] South African Parliament, Medicines and Related Substances Act No. 101 of 1965 as Amended, Government Gazette, 28 July 2017, p. 41009.

[32] General Regulations to the Medicines and Related Substances Act 101 of 1965 as Amended, 25 August 2017. Government Notice 859 in Government Gazette 41064.

[33] PIC/S Scheme: [Internet] https://picscheme.org/en/picscheme.

[34] South African Health, Products Regulatory Authority: 4.01 SA Guide to Good Manufacturing Practice, July 2019.

[35] South African Parliament, Genetically Modified Organisms Act No. 15 of 1997, Gazette No. 18029 Dated 23 May 1997 and Proclaimed in Proclamation R122, Gazette 20643, 26 November 1999.

[36] South African Parliament, National Health Act No. 61 of 2003 as Amended by Act 12 of 2013 and Proclaimed in Proclamation 38, Gazette No. 37730, 10 June 2014.

[37] Regulations Relating to the Artificial Fertilisation of Persons in Government Notice R. 175 of Government Gazette 35099 Dated 2 March 2012.

[38] Regulations Relating to the Use of Human Biological Material in Government Notice R. 177 of Government Gazette 35099 Dated 2 March 2012.

[39] Regulations Relating to Blood and Blood Products in Government Notice R. 179 of Government Gazette 35099 Dated 2 March 2012.

[40] Regulations Regarding the General Control of Human Bodies, Tissue Blood, Blood Products and Gametes in Government Notice R.180 of Government Gazette 35099 Dated 2 March 2012 and Amended by Government Notice 392 in Government Gazette 40816 Dated 26 April 2017.

[41] Regulations Relating to the Import and Export of Human Tissue, Blood, Blood Products, Cultured Cells, Stem Cells, Embryos, Foetal Tissue, Zygotes and Gametes in Government Notice R.181 of Government Gazette 35099 Dated 2 March 2012.

[42] Regulations Relating to Tissue Banks in Government Notice R. 182 of Government Gazette 35099 Dated 2 March 2012.

[43] Regulations Relating to Stem Cell Banks in Government Notice R. 183 in Government Gazette 35099 Dated 2 March 2012.

[44] ICH [Internet], https://www.ich.org/.

[45] M.S. Pepper, Partial relief from the regulatory vacuum involving human tissues through the enactment of chapter 8 of the National Health Act and regulations to it. South African Medical Journal [Internet], South Afr. Med. Assoc. NPC 102 (9) (2012 28 June) 736, https://doi.org/10.7196/samj.5940. Available from:.

[46] M. Skeen, C. Eksteen, M. Pepper, Stem cell tourism and spinal cord injury in South Africa, South Afr. Med. J. 109 (8b) (2019) 17–23, https://doi.org/10.7196/SAMJ.2019.v109i8b.13824.

[47] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 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 (Text with EEA relevance) [Internet] [cited: 3 February 2022] Available from http://data.europa.eu/eli/reg/2004/726/oj.

[48] European Parliament: Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. [Internet] [cited 3 February 2022] http://data.europa.eu/eli/dir/2001/83/2021-05-26.

[49] Department of Health, South African Good Clinical Practice: Clinical Trial Guidelines Pretoria, third ed., 2020. South Africa.

[50] Department of Health, Ethics in Health Research: Principles, Processes and Structures, second ed., 2015.

[51] C. Mason, P. Dunnill, A brief definition of regenerative medicine, Regen. Med. 3 (1) (2008) 1–5, https://doi.org/10.2217/17460751.3.1.1. ISSN 1746-0751. PMID 18154457.

[52] Mayo Clinic: Center For Regenerative Medicine [Internet] [cited 3 February 2022] https://www.mayo.edu/research/centers-programs/center-regenerative-medicine/about.

[53] U.S. Congress: Title 42 U.S.C. Chapter 6A public health service Act (Codified Version).: Available from the govinfo.gov website: https://www.govinfo.gov/app/details/USCODE-2017-title42/USCODE-2017-title42-chap6A [Internet] [Cited 22 February 2022].

[54] U.S. Congress: Title 21 U.S.C. Chapter 9 Federal Food, drug, and Cosmetic Act

(Codified Version).: Available from the govinfo.gov website: https://www.govinfo.gov/app/details/USCODE-2017-title21/USCODE-2017-title21-chap9 [Internet] [Cited 22 February 2022].
[55] Government of Japan, The Pharmaceuticals and Medical Devices Act (The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, etc.), 1960. Act No. 145. [in Japanese].
[56] Australian Government, Federal register of legislation: therapeutic goods Act 1989 (No.21, 1990), (Compilation No. 81; 1 September 2021) [Internet] [cited 3 February 2022] Website: https://www.legislation.gov.au/.
[57] EMA: EMA/200482/2020 Zolgensma EPAR public Assessment report 11 January 2019 [Internet] [cited: 3 February 2022] Available from: https://www.ema.europa.eu/documents/assessment-report/zolgensma-epar-public-assessment-report_en.pdf.
[58] EMA: EMA/CHMP/700911/2018 Luxturna EPAR public Assessment report 26 March 2020 [Internet] [cited: 3 February 2022] Available from: https://www.ema.europa.eu/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf.
[59] I. Hernandez, V. Prasad, W.F. Gellad, Total costs of chimeric antigen receptor T-cell immunotherapy, JAMA Oncol. 4 (7) (2018) 994–996, https://doi.org/10.1001/jamaoncol.2018.0977.
[60] D. Coppens, J. Hoekman, M.L. De Bruin, I. Slaper-Cortenbach, H. Leufkens, P. Meij, H. Gardarsdottir, Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries, Cytotherapy 22 (10) (2020) 592–600, https://doi.org/10.1016/j.jcyt.2020.04.092.
[61] C.L. Hendricks, M. Alessandrini, M.S. Pepper, Equitable access to cell and gene therapies in South Africa: opportunities and hurdles, Gene Ther. (2022), https://doi.org/10.1038/s41434-021-00309-y. Advance online publication.
[62] I.M. Viljoen, M.S. Pepper, When cells become medicines: a South African perspective [Internet], South Afr. Med. J. 111 (11) (2021) 1055–1059, https://doi.org/10.7196/SAMJ.2021.v111i11.15990 [cited: 3 February 2022] Available from:.
[63] PIC/S: Guide to Good Manufacturing Practice for Medicinal Products Annex 2A PE 009-16 Manufacture of Advanced Therapy Medicinal Products for Human Use, 1 February 2022.
[64] EMA: EMEA/CHMP/410869/2006 on guideline on human cell-based medicinal products, [Internet] [cited: 3 February 2022] Available from:https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-human-cell-based-medicinal-products_en.pdf.
[65] EMA: quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells [Internet] [cited: 3 February 2022] Available from:https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically-modified_en-0.pdf.
[66] EMA: guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials [Internet] [cited: 3 February 2022] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy_en.pdf.
[67] EMA: EMEA/CHMP/SWP/28367/07 Rev. 1 Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products 20 July 2017 trials [Internet] [cited: 3 February 2022] Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf.
[68] ICH: ICH Q5D Derivation and characterisation of cell substrates used for the production of biotechnological/biological products. [Internet] [cited: 3 February 2022] Available from: https://database.ich.org/sites/default/files/Q5D%20Guideline.pdf.
[69] EDQM: European Pharmacopoeia (Ph. Eur.) 10th Edition, Ph. Eur 5.2.12 on Raw materials of biological origin for the production of cell-based and gene therapy medicinal products. [Internet] [cited: 3 February 2022] Available from: https://www.edqm.eu/en/european-pharmacopoeia-ph-eur-10th-edition (subscription required).
[70] FDA 21 CFR: 21 CFR Part 1271 Subpart D – current good tissue Practice [Internet] [cited: 3 February 2022] Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-L/part-1271/subpart-D?toc=1.
[71] The United States Pharmacopoeial Convention: ⟨1043⟩ Ancillary materials for cell, gene, and tissue-engineered products. [Internet] [cited: 3 February 2022] Available from: https://doi.usp.org/USPNF/USPNF_M620_02_01.html (subscription required).
[72] EMA: EMA/CHMP/BWP/271475/2006 Guideline on potency testing of cell-based immunotherapy medicinal products for the treatment of cancer. [Internet] [cited: 3 February 2022] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-potency-testing-cell-based-immunotherapy-medicinal-products-treatment-cancer-revision-1_en.pdf.
[73] ICH: ICH Topic Q5B Note for guidance on the quality of biotechnological products: analysis of the expression construct in cell lines used for the production of r-DNA derived protein products [Internet] [cited: 3 February 2022] Available from:https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-b-analysis-expression-construct-cell-lines-used-production-r-dna-derived-protein-products_en.pdf.