IPRP
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International Regulatory Frameworks for Cell and Gene Therapies

Introduction

Cell and gene therapy products are rapidly entering the global market. These products pose unique regulatory challenges for product developers with respect to meeting regulatory requirements for many regions. In this document the IPRP Cell Therapy and Gene Therapy Working Groups present regulatory frameworks that apply to cell therapies, cell and tissue-based therapies, gene therapies, and tissue engineered products, to assist product developers in accessing global regulatory requirements for cell and gene therapies. This document will be revised as regulatory frameworks evolve. The information contained here is current as of 12 July 2021.

Disclaimer

This document reflects the views of subject matter experts participating in the IPRP Cell Therapy and Gene Therapy Working Groups and should not be construed to represent the official views of any given regulatory authority participating in the IPRP.

Country Regulatory Authority	Law/Regulation	Details	Weblinks
Australia Therapeutic Goods Administration (TGA)	Therapeutic Goods Act Therapeutic Goods Regulations	Biologics- cell and gene-modified cells	https://www.legislation.gov.au/Details/C2019C00066 https://www.legislation.gov.au/Details/F2019C00031
	Standards	Donor screening Therapeutic Goods Order (TGO 88) and labelling (TGO 87) standards	https://www.tga.gov.au/therapeutic-goods-orders
	Determination	Excluded cell therapy products	https://www.legislation.gov.au/Details/F2021C00176

Country Regulatory Authority	Law/Regulation	Details	Weblinks
Brasil Agência National de Vigilância Sanitâria (ANVISA)	RDC 214/2018 - Good Cell Practices	Requirements for Good Cell Practices	http://antigo.anvisa.gov.br/documents/10181/3078078/%281%29RDC+nº+214_2018+-+English.pdf/335b2209-76a6-4813-b4da-3f20d7a5b372
	RDC 260/2018 – Clinical Trials for ATMP	Requirements for conducting clinical trials with investigational ATMP	http://antigo.anvisa.gov.br/documents/10181/3428326/RDC+nº+260_2018++English_Version.pdf/b45120a2-501f-4c52-be8d-daf777494fd6
	RDC 338/2020 – Marketing authorization for ATMP	Requirements for ATMP marketing authorization	http://antigo.anvisa.gov.br/documents/10181/3086545/RDC_338_2020_Inglês.pdf/a2f6d2ea-9ec9-4407-b9fa-a77a3d1ca64a

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Canada Health Canada	Food and Drugs Act R.S.C., 1985, C. F-27	General requirements for cell and gene therapies. Four sets of regulations relevant to cell and gene therapies. (1) The Food and Drug Regulations (2) The Safety of Human Cells, Tissues and Organs for Transplantation Regulations (3) Medical Device Regulations (4) The Blood Regulations	https://laws-lois.justice.gc.ca/eng/acts/F-27/index.html
	(1) Food and Drug Regulations C.R.C., c. 870	Requirements for clinical investigation and authorization of drugs	https://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html
	(2) Safety of Cells, Tissues and Organs for Transplantation Regulations (CTO)	CTO Regs apply to all individuals and establishments that handle, process, distribute or import human organs, or minimally manipulated cells and tissues for homologous use, for transplantation in another individual in Canada.	https://laws-lois.justice.gc.ca/eng/regulations/sor-2007-118/page-1.html
	(3) Medical Devices Regulations (MDR)	These regulations are relevant as novel processing/manufacturing technologies are increasingly being used to process cells and to manufacture gene and cell therapy products close to the bedside by physicians. Some of these manufacturing technologies have been classified as devices.	https://laws-lois.justice.gc.ca/eng/regulations/SOR-98-282/index.html

		Drug-Device Combination Product - Is a therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or a device), such that the distinctive nature of the drug component and device component is integrated in a singular product. A combination product is subject to either the Medical Devices Regulations or the Food and Drug Regulations according to the principal mechanism of action by which the claimed effect or purpose is achieved.	https://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html or https://laws-lois.justice.gc.ca/eng/regulations/SOR-98-282/index.html
	(4) Blood Regulations	Blood Regulations are applicable for blood collected and used in the manufacture of an allogeneic drug product	https://laws-lois.justice.gc.ca/eng/regulations/SOR-2013-178/index.html
	(5) Advanced Therapy Products Pathway	Advanced Therapeutic Products (ATPs) are drugs and/or devices so unique, complex and distinct that our existing regulatory frameworks and enforcement tools are not equipped to handle them. Changes to the *Food and Drugs Act* in June 2019 enabled Health Canada to create a new legislative pathway to authorize ATPs. The	https://www.canada.ca/en/health-canada/corporate/about-health-canada/activities-responsibilities/strategies-initiatives/health-products-food-regulatory-modernization/advanced-therapeutic-products.html

		use of tailored requirements will address a product's unique characteristics while maintaining Health Canada's high standards for patient safety. A collaborative and iterative approach with a wide variety of stakeholders, upfront and throughout, will be used for the implementation of the ATP pathway.	

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Chinese Taipei - Taiwan Food and Drug Administration (TFDA)	Pharmaceutical Affairs Act	Biologics-includes cell and gene therapy products	https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0030001
	Regulations for Registration of Medical Products	Registration for all pharmaceutical products, including cell and gene therapy products	https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0030057
	Regulation Governing the Application of Specific Medical Examination Technique and Medical Device	Includes the regulation for conducting listed cell therapies at authorized medical institutes (Chapter 2 Section 1,and Table 3; Chinese version only)	https://law.moj.gov.tw/LawClass/LawAll.aspx?pcode=L0020075
	Good Human Cell and Tissue Practice	Regulate quality and data integrity of cell processing facility	https://mohwlaw.mohw.gov.tw/FLAW/FLAWDAT0201.aspx?lsid=FL022759

Country Regulatory Authority	Law/Regulation	Details	Weblinks
European Commission-European Union European Medicines Agency (EMA)	Regulation 1394/2007 on ATMPs	'Lex specialis' (only describing what is specific for ATMP)	https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf
	Directive 2001/83/EC	Main pharmaceutical legislation	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20121116&from=EN
	Regulation (EC) 726/2004	Regulation on the centralized evaluation procedure and EMA	https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF
	Directive 2009/120/EC	Scientific and technical requirements for ATMPs (dossier requirements)	https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:242:0003:0012:EN:PDF

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Israel Enforcement and Pharmaceutical Division, Ministry of Health	Public Health Regulations (clinical trials in human subjects) (1980)	General provision, includes definitions of clinical trials, dedicated committees (including superior committee responsible for genetic issues)	https://www.health.gov.il/LegislationLibrary/Briut18.pdf
	Pharmacists Ordinance [New Version], 1981	General provision, includes definition of medicinal product to include Advanced Therapies	https://www.health.gov.il/legislationlibrary/rokhut23.pdf

	The Pharmacists Regulations (Medicinal products) 1986	General provision, for licensing, registering and renewal of medicinal products Marketing Authorizations	https://www.health.gov.il/LegislationLibrary/Rokhut04.pdf
	Pharmacist Regulations (Good Manufacturing Practice for Medicinal Products) 2008	General provision, GMP regulation (in accordance with EU GMP legislation)	https://www.health.gov.il/LegislationLibrary/Rokhut27.pdf
	Cord Blood -Law and Regulation (2012)	For control and licensing of public and private Cord Blood Banks	https://www.health.gov.il/LegislationLibrary/Dam02.pdf https://www.health.gov.il/LegislationLibrary/Dam01.pdf
	Notice on the approval of general director according to pharmacist regulation (2016)	For use of Unlicensed medicines, to include Hospital Exemption	https://www.health.gov.il/LegislationLibrary/Rokhut31.pdf

Country Regulatory Authority	Law/Regulation	Details	Weblinks
Japan **Ministry of Health, Labor and Welfare/Pharmaceutical Medical Devices Agency (MHLW/PMDA)**	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Pharmaceuticals and Medical Device Act)	Defines" Regenerative Medical Products" and allows "conditional and time-limited" approval for some of the products.	http://www.japaneselawtranslation.go.jp/law/?re=02
	Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms	Regulates manufacture and use of gene-modified organisms (before marketing authorization).	https://www.biodic.go.jp/bch/english/law.html

	(Cartagena Protocol Domestic Law, Cartagena Law)		
	Act on Safety of Regenerative Medicine (regulated by MHLW, and PMDA's role is limited to inspection of the structure and equipment of contract CPC facilities)	Regulates regenerative medicine in medical practice and cell therapy CPCs outside of PMD Act (ie without intention of product registration for marketing).	https://www.mhlw.go.jp/english/policy/health-medical/medical-care/ (see the pdf file for Regenerative Medicine) see also Tobita, et al. Regenerative Therapy. 4 (2016) 78e81 (https://doi.org/10.1016/j.reth.2016.04.001)
	Standards for Biological Material (Ministerial Ordinance to supplement PMD Act)		https://www.pmda.go.jp/files/000223393.pdf

Country Regulatory Authority	Law/Regulation	Details	Weblinks
Mexico Comision Federal Para La Proteccion Contra Riesgos Sanitarios (COFEPRIS)	General Health Law, Title fourteenth (All title) Main regulation: Art. 314 Definitions Art. 315 Establishment that require license to operate Art.316 Bis 1: Blood and components Art. 318: Embryo and germ cells 321 bis: stem cell donation CHAPTER III BIS Disposition of blood, blood components, human blood products and stem cells.	For quality specifications and review procedures for drug substance, drug product and excipients, COFEPRIS can use information from Pharmacopeia from other countries (Regulation for Health products, article 8). COFEPRIS can wield the sanitary control for health products under the terms of the Law, the international instruments and other applicable	http://www.diputados.gob.mx/LeyesBiblio/pdf_mov/Ley_General_de_Salud.pdf Note: The General Health Law and Regulation for Health products are undergoing many changes during this administration. Sometimes the updates are only available in the Official Journal of the Federation: https://www.dof.gob.mx/ COFEPRIS website also provides a specific link for the legal framework: https://www.gob.mx/cofepris/acciones-y-programas/marco-juridico-de-la-cofepris?state=published

	Art. 342 Bis 3. National registry for Blood Stem cells	provisions (Regulation for the Federal Commission for protection against sanitary risk).	*This link is an unofficial website, COFEPRIS is not responsible for the content: https://www.olivares.mx/product-regulation-and-liability-in-mexico/*
	Regulation for Health Products Chapter III Registry	General requirements for the marketing authorization for medicinal products For quality specifications and review procedures for drug substance, drug product and excipients, COFEPRIS can use information from Pharmacopeia from other countries (Regulation for Health products, article 8). COFEPRIS can wield the sanitary control for health products under the terms of the Law, the international instruments and other applicable provisions (Regulation for the Federal Commission for protection against sanitary risk).	COFEPRIS website also provides an specific link for the legal framework: https://www.gob.mx/cofepris/acciones-y-programas/marco-juridico-de-la-cofepris?state=published
	Official Mexican Standard NOM-059-SSA1-2015, Good manufacturing practices for medicinal products	GMP for medicinal products	

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Republic of Korea Ministry of Food and Drug Safety (MFDS)	Pharmaceutical Affairs Act	To prescribe matters necessary to deal with pharmaceutical affairs	http://law.go.kr/LSW/eng/engMain.do
	Act on the Safety of and Support for Advanced Regenerative Medicine and Advanced Biopharmaceuticals	To prepare concrete procedure and details for the implementation of whole life-cycle safety management for advanced biopharmaceuticals and clinical research on advanced regenerative medicine	http://law.go.kr (English version is not yet available.)
	Enforcement Decree of the Safety of and Support for Advanced Regenerative Medicine and Advanced Biopharmaceuticals	To prescribe the matters mandated by the safety of and support for advanced regenerative medicine and advanced biopharmaceuticals Act and those necessary for enforcing said Act affairs.	http://law.go.kr (English version is not yet available.)
	Regulation on the Safety of and Support for Advanced Biopharmaceuticals	To prescribe matters delegated by the safety of and support for advanced	http://law.go.kr (English version is not yet available.)

		biopharmaceuticals Act and the Enforcement Decree of the safety of and support for advanced biopharmaceuticals Act and matters necessary for their enforcement.	
	Regulation on Approval and Review of Advanced Biopharmaceuticals	For improvement the efficiency of review and approval processes and promote the advanced biopharmaceutical products that have been developed using new technologies.	http://law.go.kr (English version is not yet available.)
	Enforcement Decree on the Standards of Facilities of Manufacturers and Importers of Medicinal Products etc.	To prescribe requirements for facilities of manufacturers and importers of medicinal products etc.	http://www.mfds.go.kr (Language: English version) Bio&Cosmetics → Regulation → Find #15
	Enforcement Regulation of the Enforcement Decree on the Standards of Facilities of Manufacturers and Importers of Medicinal Products etc.	To prescribe requirements and procedures delegated by the Enforcement Decree on Standards of Facilities of Manufacturers and Importers of Medicinal Products, etc.	http://www.mfds.go.kr (Language: English version) Bio&Cosmetics → Regulation → Find #16

	Regulation on Safety of Medicinal Products, etc.	To prescribe matters delegated by the Pharmaceutical Affairs Act and the Enforcement Decree of the Pharmaceutical Affairs Act and matters necessary for their enforcement.	http://www.mfds.go.kr (Language: English version) Bio&Cosmetics → Regulation → Find #14
	Regulation on Pharmaceutical GMP	To assure appropriate Pharmaceutical GMP by specifying detailed requirements for enforcement of Regulation on Safety of Medicinal Products, etc and detailed requirements for expiry period of certificate of GMP compliance of a manufacturer for medicinal products under application for product approval.	http://www.mfds.go.kr (Language: English version) Bio&Cosmetics → Regulation → Find #18
	Regulation on Approval for Investigational New Drug Application of Drugs	To set force the detailed matters regarding the preparation tip, scope, requirement, and exemption scope of data necessary for IND application, approval	http://www.mfds.go.kr (Language: English version) Bio&Cosmetics → Regulation → Find #22

		procedure, and standard, and to ensure that appropriate measures are used in conjunction with the Investigational new drug (IND) approval processes.	
	Regulation on Fees for Pharmaceutical Approval etc.		http://www.mfds.go.kr (Language: English version) Bio&Cosmetics → Regulation → Find #28
	Regulation on Approval and Review of Biological Products	For improvement the efficiency of review and approval processes and promote the biological products that have been developed using new technologies.	http://www.mfds.go.kr (Language: English version) Bio&Cosmetics → Regulation → Find #32
	Korean Pharmacopeia		http://www.law.go.kr/행정규칙/대한민국약전/(2019-11,20190228)

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Saudi Arabia **Saudi Food and Drug Authority (MENA Region)**	Notification and documentation of proposed clinical trial /Submission of ddeclaration that no enrichment or culturing is used during this procedure.	This regulation is applied for well established procedures. Clinical trial applications for Hematopoietic Progenitor Stem Cell (HPC) Transplantation, and	www.sfda.gov.sa

		Non-Myeloablative Conditioning and Transplantation of Partially HLA-Mismatched and HLA-Matched Bone Marrow followed this regulation.	
	Notification and documentation of proposed clinical trial /Submission of procedural steps	This regulation is applied for clinical trial applications regarding aamniotic membrane harvested from placenta of healthy women delivered by elective cesarean section.	

Country Regulatory Authority	Law/Regulation	Details	Weblinks
Singapore **Health Sciences Authority (HSA)**	Cell, Tissue and Gene Therapy Products (CTGTP) Regulations under the Health Products Act	The regulations cover both lower risk (minimally manipulated for homologous use that are not combined with therapeutic product or medical devices) and higher risk CTGTPs, from clinical trials, registration, manufacture, import, supply to post-market duties and obligations.	https://www.hsa.gov.sg/ctgtp

Country Regulatory Authority	Law/Regulation	Details	Weblinks
Switzerland Swissmedic	Swiss Transplantation Act and the Swiss Therapeutic Product Act (TPA)	No marketing authorization but notification of all activities at Swissmedic such as manufacturing, storage, import/export/, wholesale, distribution etc. Applicable only in case the cells and tissue are defined as Transplants – (non-substantial manipulation according EU Regulation ATMP's and homologous use). Some examples: • Fat Stems Cells, Stromal Vascular Fraction (from Liposuction without substantial manipulation such for ex. enzymatic digestion or from Devices such as Lipogem etc.) • Blood Stem cells from umbilical cord, bone marrow or peripheral blood)	https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/besondere-arzneimittelgruppen--ham-/transplant-products.html

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United States Food and Drug Administration (US FDA)	21 CFR 1271 Tissue Regulations	Tissue Rules intended to prevent the spread of infectious disease (Donor eligibility) Applicable to cell therapy, gene therapy, tissue engineered products	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=1271.10
	21 CFR 600 -690 Biological License Applications (BLA) Requirements	Applicable to all biologics including cell therapy, gene therapy, tissue engineered products	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=600

	21 CFR 312 Investigation New Drug (IND) Requirements	Applicable to all biologics including cell therapy, gene therapy, tissue engineered products	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=312
	21 CFR 210 Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs	Applicable to all biologics including cell therapy, gene therapy, tissue engineered products	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=210
	21 CFR 211 Current Good manufacturing practices for finished pharmaceuticals	Applicable to all biologics including cell therapy, gene therapy, tissue engineered products	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211
	21 CFR 314.126 Clinical Trial Standards	Applicable to all biologics including cell therapy, gene therapy, tissue engineered products	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.126
	21 CFR 812 Investigational Device Exemption (IDE) Requirements	Applicable to devices	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812
	21 CFR 814 Pre-market approval (PMA)/Humanitarian Device Exemption (HDE) Regulations	Applicable to devices	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820
	21 CFR 820 Quality Systems Regulation/Good Manufacturing Practices	Applicable to devices	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820
		Applicable to devices	https://www.govinfo.gov/content/pkg/CFR-2015-title21-vol8/pdf/CFR-2015-title21-vol8-part807-subpartE.pdf