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International Pharmaceutical Regulators Forum

Cell Therapy Working Group

Meeting Summary

International Regulatory Perspectives: Degree of Regulatory Oversight for Eight Categories of Cell Therapy Products

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Introduction

The International Pharmaceutical Regulators Forum – Cell Therapy Working Group (IPRF-CTWG) was formed to provide a forum for international regulatory authorities to share information on best practices for the regulation of cellular therapy products, and to assess potential areas for international regulatory convergence. Advancements in cell therapy technologies and resulting products pose unique challenges to regulatory agencies around the globe; therefore, it is considered important to learn from one another how to best enable access to these emerging therapies while mitigating the potential risks that they pose.

This article communicates findings from a meeting in Auckland, New Zealand, where an international discussion was held on April 26, 2013. The meeting provided an opportunity for the international community to reflect upon national regulatory frameworks for cell therapies and to develop a snapshot comparison of these frameworks.

Background

Cell therapy products represent an emerging class of products manufactured from human cells and tissues using a wide variety of processing techniques to treat various conditions and diseases. Prior to April 26, 2013, the IPRF-CTWG discussed how these products are regulated by different regulators internationally. These early discussions identified the importance of legislative definitions and highlighted how different definitions effect classification decisions, regulatory pathways, submission requirements, and establishment licensing / certification requirements. IPRF-CTWG participants were

Most regulatory authorities classify cell therapy products on factors such as their degree of manipulation / processing (e.g. “high/low” or “substantial/minimal”); their proposed use (e.g. “homologous/non-homologous”); and whether the cells used are autologous or allogeneic. Some regulatory authorities consider other or additional factors, such as who is preparing the cell (e.g. a manufacturer for general distribution versus a physician for a single patient or whether the product is used for clinical research or clinical trials.

convinced that a broader perspective (focussing on regulatory approaches instead of details about regulatory frameworks) would help to identify potential avenues for international regulatory convergence.

With a goal to identify commonalities in regulatory approaches, representatives of nine different regulatory agencies were asked to generally characterise their own regulatory frameworks for eight categories of cellular products. These categories were determined based on the following three key variables, which are characteristics generally accepted to be important for cell therapy classification: Degree of cell manipulation, proposed use of the cells, and autologous or allogeneic source of cells.

Regulatory frameworks were broadly characterised as follows: (1) no regulatory oversight (henceforth "none"); (2) attestation / certification / conformance to a standard with no pre-market review and authorization (henceforth "limited"); or (3) pre-market review and authorization schemes (henceforth "full"). Regulatory authorities were asked to indicate which of these levels of regulatory oversight applied to each of the eight categories, if the cell product was in the investigational use stage versus marketed use stage. The results would complete the following table, which could help to form more objective analyses:

Table 1 - Categories used to assess the degree of regulatory oversight.

Category of Product	*Source*	*Degree of Manipulation*	*Intended Use*	*Degree of Oversight* (1,2,3)*	
				Investigational	*Market Use*
Category A	Autologous	Minimal	Homologous		
Category B	Autologous	Substantial	Non-homologous		
Category C	Autologous	Minimal	Non-homologous		
Category D	Autologous	Substantial	Homologous		
Category E	Allogeneic	Minimal	Homologous		
Category F	Allogeneic	Substantial	Homologous		
Category G	Allogeneic	Minimal	Non-homologous		
Category H	Allogeneic	Substantial	Non-homologous		

***note – Table 3 provides examples of cell therapy products in each category**

Benefits and Limitations of the Categorization Effort

From a policy and international convergence perspective, this basic categorization effort is important. The benefit of categorizing cell therapies based on key characteristics is that it will allow identification of commonalities in levels of regulatory oversight for specific groups of cell therapy products even where the differences in specific products or respective legislative frameworks may appear significant.

The aim of these efforts is hampered by the fact that products in the same category are not always regulated in the same manner, and this exercise cannot be used to support regulatory classification or review decisions.

Results

The following summary is provided based on details provided by the participating regulatory agencies in presentations at the IPRF-CTG meeting in New Zealand on April 26, 2013 and from follow-up activities with those regulatory agencies for the purposes of comparing regulatory approaches.

Table 2 (Results) - Degree of regulatory oversight (1 = none, 2= some, 3 = full) for investigational and market use of products in categories A-H for each jurisdiction.

	Category A		
	Investigational	*Market Use*	
US FDA	2	2	*Autologous Min. manipulated Homologous*
Singapore HSA	1	1	
EU EMA	2	2	
Health Canada	3	1	
Korea MFDS	3	3	
Japan PMDA	2	2	
Chinese Taipei FDA	2	2	
Australian TGA	2	2	
NZ Medsafe	1	1	

	Category E		
	Investigational	*Market Use*	
US FDA	3	3	*Allogeneic Min. manipulated Homologous*
Singapore HSA	1	1	
EU EMA	2	2	
Health Canada	3	2	
Korea MFDS	3	3	
Japan PMDA	2	2	
Chinese Taipei FDA	2	2	
Australian TGA	2	3	
NZ Medsafe	3	3	

	Category B		
	Investigational	*Market Use*	
US FDA	3	3	*Autologous Manipulated Non-homologous*
Singapore HSA	3	3	
EU EMA	3	3	
Health Canada	3	3	
Korea MFDS	3	3	
Japan PMDA	3	3	
Chinese Taipei FDA	3	3	
Australian TGA	2	3	
NZ Medsafe	3	3	

	Category F		
	Investigational	*Market Use*	
US FDA	3	3	*Allogeneic Manipulated Homologous*
Singapore HSA	3	3	
EU EMA	3	3	
Health Canada	3	3	
Korea MFDS	3	3	
Japan PMDA	3	3	
Chinese Taipei FDA	3	3	
Australian TGA	2	3	
NZ Medsafe	3	2	

	Category C		
	Investigational	*Market Use*	
US FDA	3	3	*Autologous Min. manipulated Non-homologous*
Singapore HSA	3	3	
EU EMA	3	3	
Health Canada	3	3	
Korea MFDS	3	3	
Japan PMDA	3	3	

	Category G		
	Investigational	*Market Use*	
US FDA	3	3	*Allogeneic Min. manipulated Non-homologous*
Singapore HSA	3	3	
EU EMA	3	3	
Health Canada	3	3	
Korea MFDS	3	3	
Japan PMDA	3	3	

Chinese Taipei FDA	3	3	
Australian TGA	2	3	
NZ Medsafe	3	3	

	Category D	
	Investigational	*Market Use*
US FDA	3	3
Singapore HSA	3	3
EU EMA	3	3
Health Canada	3	3
Korea MFDS	3	3
Japan PMDA	3	3
Chinese Taipei FDA	3	3
Australian TGA	2	3
NZ Medsafe	3	2

Autologous Manipulated Homologous

Chinese Taipei FDA	3	3	
Australian TGA	2	3	
NZ Medsafe	3	3	

	Category H	
	Investigational	*Market Use*
US FDA	3	3
Singapore HSA	3	3
EU EMA	3	3
Health Canada	3	3
Korea MFDS	3	3
Japan PMDA	3	3
Chinese Taipei FDA	3	3
Australian TGA	2	3
NZ Medsafe	3	3

Allogeneic Manipulated Non-homologous

Figure 1 (Results)- Comparison of responses on the degree of regulatory oversight for investigational use of cell therapy products in categories A-H

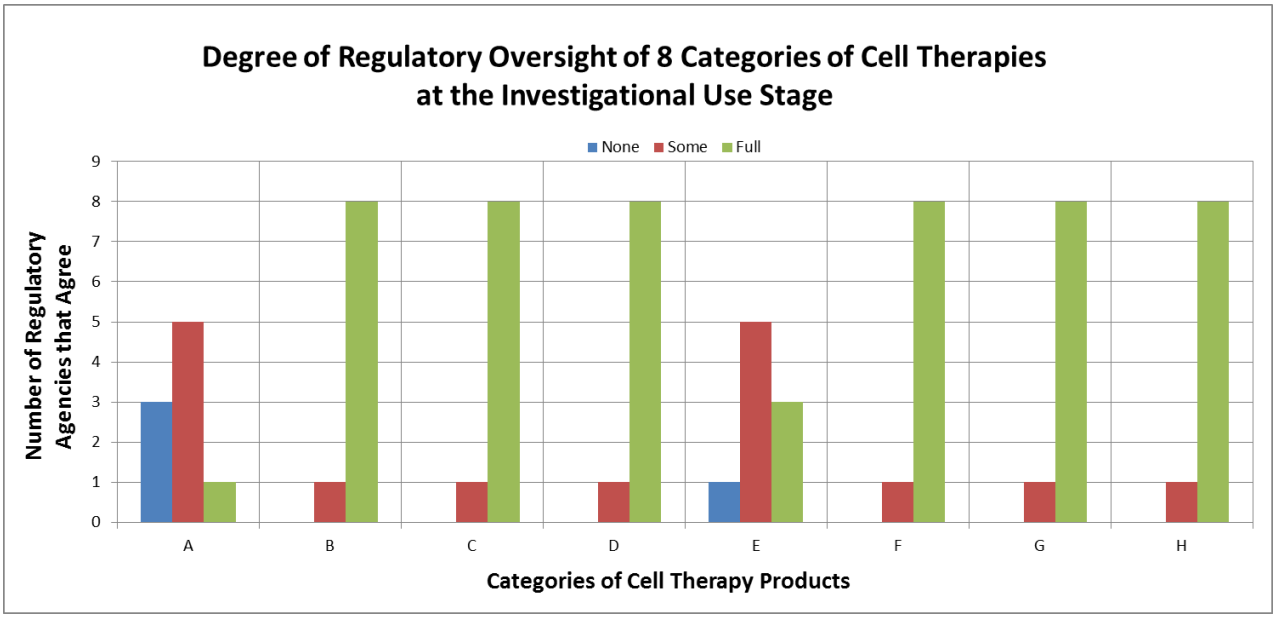
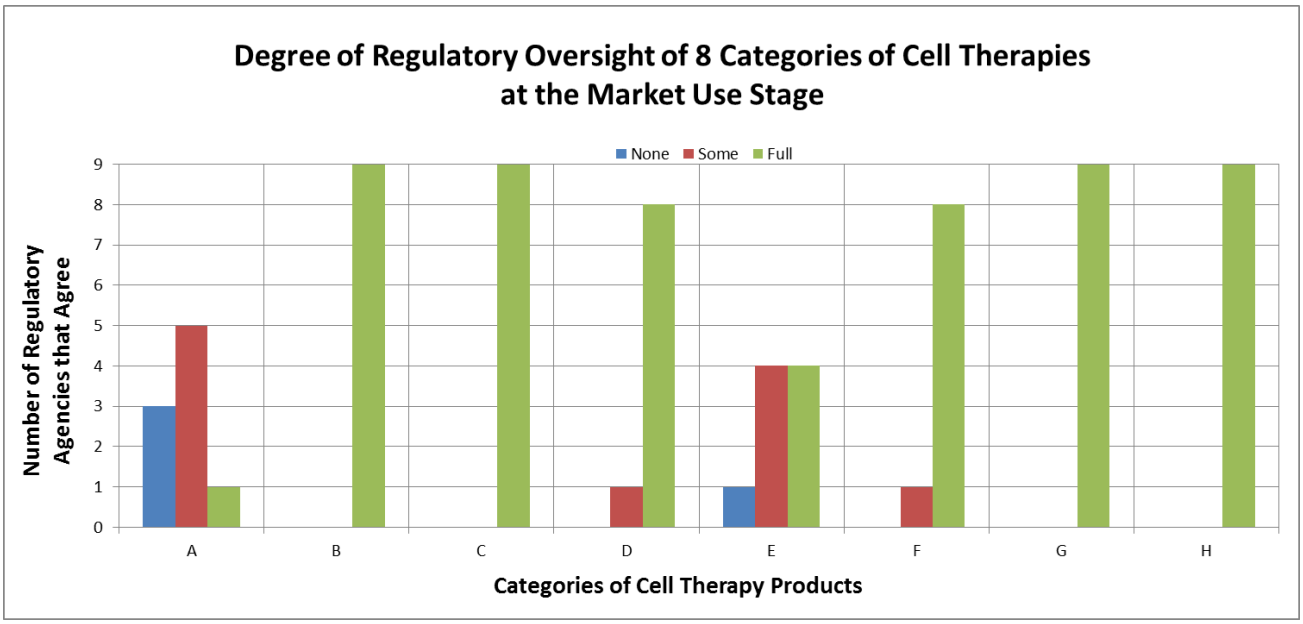


Figure 2: Comparison of responses on the degree of regulatory oversight for market use of cell therapy products in categorised A-H.



"Non-homologous use" universally requires regulatory oversight

As illustrated in Figures 1 and 2, a high degree of agreement is found surrounding the regulation of non-homologous use of cell therapy products at both stages of development (non-homologous use products are represented by Categories BCGH). In Figure 1, eight (8) out of nine (9) regulatory agencies agreed that all non-homologous use products require pre-market regulatory oversight prior to investigational use. In figure 2, nine (9) out of nine (9) regulatory agencies agreed that all cell therapies that are intended for non-homologous purposes require pre-market review and authorization prior to market use.

For this reason, it could be argued that the best predictor of full regulatory oversight is non-homologous use. Known risks associated with non-homologous use include cell migration, growth of ectopic tissues and tumourigenicity. These known risks must be considered in addition to unknown risks that may be associated with the administration of relatively large number of cells into an environment that is not natural concerning the cell type and dose, and then balanced against potential benefits. For this reason, full pre-market review for both safety and effectiveness can be considered appropriate risk mitigation strategies of regulatory agencies.

More variation is found in the regulation of homologous use products, as shown in Figures 1 and 2 (homologous use products are represented by Categories ADEF). When a cell product is for homologous use, the other criterion for classification, degree of manipulation and autologous or allogeneic cell source, determine the degree of regulatory oversight, as discussed below.

"Substantial manipulation" generally requires regulatory oversight

As illustrated in the Figures 1 and 2, near complete agreement is found amongst regulatory authorities with respect to the degree of regulatory oversight of substantially manipulated cell therapies (substantially manipulated products are represented by Categories BDFH). At the

investigational stage, eight (8) out of nine (9) regulatory agencies agreed that all of these substantially manipulated products require pre-market review and authorization prior to investigational use. At the market authorization stage, all regulatory agencies agreed that substantially manipulated cell therapies for non-homologous use require full pre-market review, while eight (8) out of nine (9) regulatory agencies agreed that that substantially manipulated for homologous use require pre-market regulatory review.

It could be argued that the risks introduced by substantial manipulation of cells for cell therapy necessitate a high degree of regulatory oversight. However, the level of manipulation may be highly variable and the definitions of substantial manipulation may be different between different jurisdictions. Known risks associated with use of substantially manipulated cells include increased immunogenicity of the altered/augmented cell, cell death (and related loss of efficacy), and risks introduced by novel processing techniques and excipients / reagents. These risks apply equally for autologous and allogeneic cells because one's own cells may be altered sufficiently to be recognised as foreign to the patient. Known risks must be considered in addition to unknown risks that may be associated with the administration cells whose characteristics have been altered, and then balanced against unknown benefits. For this reason, limited or full premarket review for both safety and effectiveness may be considered appropriate risk mitigation strategies of regulatory agencies.

As shown in Figures 1 and 2, more variation is found in the level of regulatory oversight of minimally manipulated cells (represented by Categories ACEG). For minimally manipulated cells, the other criteria for classification (namely whether the proposed use is homologous or non-homologous; and whether the cell source is either autologous or allogeneic) determine the degree of regulatory oversight. The most variation in the level of regulatory oversight was observed for minimally manipulated cells that were autologous and for homologous use (Category A) or allogeneic and for homologous use (Category E)

Allogeneic or autologous sources have less impact than other criteria on the level of regulatory oversight

As illustrated in Figures 1 and 2, no clear pattern distinguishing autologous cell therapies (represented by Categories ABCD) from allogeneic cell therapies (represented by Categories EFGH) is apparent. For this reason it may be suggested that the source of cells (allogeneic vs autologous) has less relative impact on its degree of regulatory oversight than the proposed use or degree of manipulation.

When comparing the effect the source of cells on regulatory oversight it is particularly difficult to identify patterns because the most variably regulated products (minimally manipulated cell therapies for homologous use in Categories A and E) are not grouped together. It is worth a note to say that Categories A and E were most challenging for regulators to identify their degree of regualtory oversight – several regulatory agencies reported some version of hospital exemptions / same surgical procedure exemptions that reflect some ability to delegate minimally manipulated cell therapies for homologous use to another jurisdiction (e.g. another level of government or professional practice). Unfortunately these exemptions could not be captured effectively by this exercise, and regulators were left with a difficult decision to select a "best fit".

Regulatory oversight is consistent between investigational and market use stages

Data were collected for both investigational and market use stages in order to assess whether regulatory agencies differed in levels of oversight at these stages. Investigational studies represent a different composition of risk than general market use – they represent proportionately more unknown risks relative to known risks. For this reason it could be assumed that there could be differences in the type of regulatory oversight of cell therapies at the investigational stage and market use stage. This appears only true in a minority of regulatory jurisdictions.

Within six (6) out of nine (9) regulatory jurisdictions the type of regulatory frameworks for all categories of cell therapy products (A through H) were the same at the investigational and market use stages of product development (US FDA, HSA, EU/EMA, MFDS PMDA, Chinese Taipei FDA).

The other three (3) out of nine (9) regulatory jurisdictions reported differences in the type of regulatory oversight between the investigational and market use stages of certain categories of products (HC, TGA, MedSafe). In Canada, minimally manipulated homologous use products (Category A and E) are subject to pre-market review at the investigational stage, but they are subject to no clear federal regulatory framework prior to general market use – these products may fall between Federal and provincial jurisdictions depending on how they are prepared for use. Similarly in New Zealand, Category D and F products are subject to full pre-market review at the investigational stage and only limited regulatory oversight at the market use stage. In EU, the use of investigational medicinal products are regulated through legislation of clinical trials and authorized by the competent authorities in member stages. For category C and G products (minimally manipulated, non-homologous use) their classification as medicinal products may not be clear to all treating physicians and they may be used to some extent in hospitals outside regulatory oversight. In Australia, all products except Category A product are subjected to limited regulatory oversight at the investigational stage, but to full pre-market review at the market use stage.

Conclusions

While differences of definition and interpretation pertaining to cellular therapies exist among regulatory agencies, the following observations have been made:

- Non-homologous use and substantial manipulation of cells generally require full pre-market regulatory review
    - All regulatory authorities require pre-market review and authorization for products intended for non-homologous use products at the market authorization stage, irrespective of the any other criteria.
    - Most regulatory authorities require pre-market review and authorization for more than minimally manipulated products, irrespective of the any other criteria.

- From an international perspective, the source of cells (autologous vs allogeneic) has less impact on the degree of regulatory oversight for cell therapies than their proposed use or degree of manipulation
- Clear differences exist in regulatory oversight of minimally manipulated cells for homologous use from autologous and allogeneic sources
    - Some regulatory authorities grant exemptions for autologous cells processed at bedside/ by hospitals
- The areas of greatest consensus, non-homologous use and substantial manipulation, may be the most productive areas of focus for future IPRF-CTG regulatory convergence activities

Table 3 Examples of Products in each category

Category A:
Autologous, Minimally Manipulated, Homologous Use

Examples*
Platelet-rich-plasma (PRP)
Lymphohematopoeitic stem cells taken from an individual before aggressive cancer therapy to reconstitute their own lymphohematopoeitic system after said therapy
Autologous peripheral blood hematopoietic stem / progenitor cells for hematologic malignancies
CD34+ selected cells / enriched cells
Autologous keratinocytes mechanically isolated from thin skin grafts and immediately applied to wound bed (burnt wounds, sites of autologous skin grafts, ulcers etc.)
Non-manipulated lipoaspirate containing adipocytes and stromal fraction for soft tissue filling
Hematopoietic stem cells (HSCs) isolated from peripheral blood, cord blood and bone marrow by centrifugation
Injection of Autologous Epidermal Cell Suspension for Patient with Vitiligo
Disclaimer: These examples represent a compilation of real and hypothetical examples from all regulatory agencies that provided responses. They are not universally agreed upon by all of the participants

Category B:

Autologous, More than Minimally Manipulated, Non-Homologous Use

Examples*
Pluripotent stem cells expanded, differentiated, seeded into autograft tissue scaffolding with claims of regenerating skin in a burn victim
Autologous isolated and culture expanded mesenchymal stem cells (e.g. from bone marrow) for cardiovascular indications (e.g. for improvement of left ventricular ejection fraction in acute myocardial infarction)
Mesenchymal stem cells isolated from fat tissue, cultured and seeded into scaffold/matrix (e.g. b-TCP) for bone repair
Autologous Somatic Stem Cells
Autologous functionally differentiated cells derived from iPS cells
Autologous adipose-derived mesenchymal stem cells for Crohn's fistula
Autologous olfactory ensheathing cells to treat patients with old, ischemic cerebrovascular attack
Treatment of sequelae caused by arteriovenous malformation hemorrhage with autologous mesenchymal stem cells
Disclaimer: These examples represent a compilation of real and hypothetical examples from all regulatory agencies that provided responses. They are not universally agreed upon by all of the participants

Category C:

Autologous, Minimally manipulated, Non-Homologous Use

Examples*
Mesenchymal stem cells derived from the stromal vascular fraction of lipoaspirate for injection into heart after heart attack to maximise healing (via cytokine activity?)
Autologous peripheral blood hematopoietic stem/progenitor cells for cardiovascular indications
Enriched peripheral blood mesenchymal stem cells for cardiac repair
Concentrate of bone marrow for treatment of atrophic, non-union bone fractures
Epithelial cells sheet isolated from the oral cavity instead of corneal sheet cells
Autologous bone marrow aspirate-centrifuged stem cells transplantation for articular cartilage defect
Autologous bone marrow monocyte-fractioned stem cells transplantation for critical limb ischemia
Autologous stromal vascular fraction for wound healing in DM patients or burn patients
Disclaimer: These examples represent a compilation of real and hypothetical examples from all regulatory agencies that provided responses. They are not universally agreed upon by all of the participants

Category D:
Autologous, More than Minimally Manipulated, Homologous Use

Examples*
Lymphohematopoietic stem cells derived from own cord blood, peripheral blood or bone marrow that are expanded to meet clinical dose for hematopoietic reconstitution
Autologous chondrocytes isolated from cartilage biopsy, expanded in culture, administered at site of cartilage defect
Autologous epithelial cells isolated from skin biopsy, expanded in culture and intended to cover burns
Cultured chondrocytes for cartilage repair
Cultured skeletal muscle cells for treatment of stress induced urinary incontinence (injection of cells to sphincter)
Autologous cultured keratinocytes
Autologous cultured cartilage
Disclaimer: These examples represent a compilation of real and hypothetical examples from all regulatory agencies that provided responses. They are not universally agreed upon by all of the participants

Category E:
Allogeneic, Minimally Manipulated, Homologous Use

Examples*
Lymphohematopoietic cells derived from centrifuged cord, peripheral blood or bone marrow for reconstitution
Basic human tissues and cells that are removed, cut / sized, dissected, centrifuged, lyophilised, sterilised, rinsed, preserved without altering relevant characteristics
Allogeneic unrelated umbilical/placental cord blood for hematologic malignancies
Allogeneic stromal vascular fraction in cell-assisted facial lipotransfer
Banked hematopoietic cells derived from cord blood derived for hematopoietic reconstitution
Banked tissues (skin, musculoskeletal, ocular, heart) for allograph
Disclaimer: These examples represent a compilation of real and hypothetical examples from all regulatory agencies that provided responses. They are not universally agreed upon by all of the participants

Category F:
Allogeneic, More than Minimally Manipulated, Homologous Use

Examples*
Lymphohematopoeitic stem cells derived from someone else's cord blood, peripheral blood or bone marrow that are expanded to meet clinical dose for hematopoeitic reconstitution
Allogeneic antigen-specific T cells expanded in culture, such as EBV-specific T cells from transplant donor for treatment of post-transplant lymphoproliferative disease
Allogeneic pancreatic islet cells used for treatment of type 1 diabetes
Cultured human dermal fibroblasts and/or keratinocytes for skin repair
Heterologous human liver cells (in perfusion device) for maintenance therapy of patients with liver failure
Allogeneic cultured cartilage
Allogeneic cultured stromal vascular fraction in cell-assisted facial lipotransfer
Disclaimer: These examples represent a compilation of real and hypothetical examples from all regulatory agencies that provided responses. They are not universally agreed upon by all of the participants

Category G:
Allogeneic, Minimally Manipulated, Non-Homologous Use

Examples*
Mesenchymal stem cells derived from someone else's stromal vascular fraction of lipoaspirate for injection into heart after heart attack to maximise healing (via cytokine activity?)
Allogeneic, non-cultured mesenchymal stem cells for treatment of GvHD
Transplantation of hematopoietic stem cells derived from someone else's cord blood for cerebral palsy
Allogeneic bone marrow transplantation for use in repairing heart disease
Disclaimer: These examples represent a compilation of real and hypothetical examples from all regulatory agencies that provided responses. They are not universally agreed upon by all of the participants

Category H:
Allogeneic, More than Minimally Manipulated, Non-Homologous Use

Examples*
Allogeneic cultured mesenchymal stem cells to treat graft-versus-host disease

Allogeneic culture expanded mesenchymal stem cells for cardiovascular indications
Allogeneic, cultured mesenchymal stem cells for treatment of rheumatoid arthritis
Expanded placenta-derived mesenchymal stem cells for treatment of Crohn´s disease, multiple sclerosis, rheumatoid arthritis
Allogeneic iPS-like Cells
Allogenic umbilical cord blood- derived mesenchymal stem cells for articular cartilage defect
Allogeneic mesenchymal stem cell transplantation in patients with cerebellar ataxia
Genetically-modified T cells/HPC cells for treatment of HIV
Disclaimer: These examples represent a compilation of real and hypothetical examples from all regulatory agencies that provided responses. They are not universally agreed upon by all of the participants

Table 3: Examples of products that may fit into categories A-H.

Relevant Regional Terminology

Below is a list of terminology with legal references for region that have established terminology relevant to the content of this manuscript.

Cell Therapy Product (KMFDS) - refers to a medicinal product manufactured through physical, chemical, and/or biological manipulation, such as in vitro culture of autologous, allogeneic, or xenogeneic cells. However, this definition does not apply to the case where a medical doctor performs minimal manipulation that does not cause safety problems of autologous or allogeneic cells in the course of surgical operation or treatment at a medical center (simple separation, washing, freezing, thawing, and other manipulations, while maintaining biological properties)[*Enforcement rule of Medicinal products Safety*].

Cell Therapy Product (Health Canada) - human cells of somatic (fetal, neonatal and adult) or embryonic origin that are used for investigative, [and therapeutic or diagnostic] purposes. This includes both cells derived from the individual undergoing treatment (autologous) as well as from donated tissues (allogeneic) and encompasses induced pluripotent stem cells or other cells in which the differentiation potential has been altered or enhanced. (*Draft guidance for Sponsors: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans*).

Somatic Cell Therapy (U.S. Food and Drug Administration)- Autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics *ex vivo* to be administered to humans and applicable to the prevention, treatment, cure, diagnosis or mitigation of disease or injuries [*U.S. Federal Registry Notice: October 14, 1993. 58 FR 53248 Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products*].

Somatic Cell Therapy (European Medicines Agency) - Biological medicinal products that:

- contain or consist of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological function or structural properties relevant for the intended clinical use have been altered, or of cell or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

- is presented as having for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through pharmacological, immunological or metabolic activity of its cells or tissues [*EU legislation: Directive 2009/120/EC*].

Cell and Tissue-Based Therapeutic Product (Singapore Health) - Cell- and tissue-based therapeutic product means a health product that contains or consists of human autologous, allogeneic or xenogeneic cell, tissue or their derivative that is:
-used for or administered to humans; or intended to be used for or administered to humans, for one or more of the following purposes or has one or more of the following effects when used in or on humans
- preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, defect, ailment, injury, or the symptoms thereof; replacing, modifying, influencing, inhibiting, restoring, correcting, altering or supporting the anatomy or of a physiological process; supporting or sustaining life; testing the susceptibility of humans to any disease or disorder; or any revision or change in human condition, including any revision or change in the appearance, colour, texture, structure or position of any bodily feature of a person including any autologous, allogeneic or xenogeneic cell, tissue or their derivative that is intended to be used in the manufacture of a cell- and tissue-based therapeutic product [*Singapore legislation*].

Substantial Manipulation (EMA) - The following manipulations are <u>not</u> considered as substantial manipulations: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation/concentration/purification, filtering, lyophilisation, freezing, cryopreservation, vitrification [*EU legislation, Regulation 1394/2007, Annex I*].

Minimal Manipulation (U.S.FDA) - (a) For structural tissue- processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, and replacement.

(b) For cells or non-structural tissue – processing that does not alter the relevant biological characteristics of cells or tissues [*US 21 CFR 1271.3 (f)*].

Minimal Manipulation (Health Canada) - (a) in respect of a structural tissue, that the processing does not alter the original characteristics that are relevant to its claimed utility for reconstruction, repair or replacement; and

(b) in respect of cells and nonstructural tissue, that the processing does not alter the biological characteristics that are relevant to their claimed utility. (*Safety of Human Cells, Tissues and Organs for Transplantation Regulations*)

Homologous Use (U.S. FDA) - Repair, replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic functions in the recipient as in the donor [*US 21 CFR 1271.3(c)*].

Homologous Use (Health Canada) - in respect of a cell, tissue or organ, means that the cell, tissue or organ performs the same basic function after transplantation (*Safety of Human Cells, Tissues and Organs for Transplantation Regulations*).