Position paper on Unproven Cell-Based Therapies: Current Global Status and Recommendations to the World Health Organization

An international and multidisciplinary group of experts representing international societies involved in stem cell transplantation, stem cell research, cell therapy and blood transfusion was convened under the auspices of the Worldwide Network for Blood and Marrow Transplantation (WBMT). WBMT is a non-governmental organization in official relations with the World Health Organization (WHO). The purpose of this position paper is to report to WHO on the scale, severity, importance and characteristics of the global cell-based industry with emphasis on unproven therapies currently being performed without adequate regulatory and ethical oversight.

Summary

Direct-to-consumer marketing of unproven cell-based interventions has progressively become a global serious public health concern. Among cell therapeutics we can broadly distinguish immune cells (unmodified or gene modified natural killer T-cells) and stem cell-based interventions. Currently, there is a limited number of both immune and stem cell products with market authorization[1] and the current state of scientific evidence does not justify the use of most cell-based interventions outside of well-designed, strictly supervised and regulated clinical research studies.

Despite this, the increase in unproven cell-based treatments has driven false hopes and expectations. Some of these unproven cell-based treatments have been associated with serious adverse events, including donor derived tumours, blindness, paralysis, immune reactions, and death. The lack of compelling evidence of therapeutic benefit suggests that the marketing and sale of such interventions is financially exploitative of a desperate and vulnerable population. Regulations have been developed in many jurisdictions, but poor harmonization and patchy enforcement remain problems. We aim here to raise the attention of WHO on the topic and its complexity, presenting a set of recommendations to WHO to support appropriate oversight of this global health matter and the development of safe and effective cell-based therapeutics.

[1]Cuende N, Rasko JEJ, Koh MBC, Dominici M, Ikonomou L. Cell, tissue and gene products with marketing authorization in 2018 worldwide. *Cytotherapy*. 2018;20(11):1401-13.

Background scientific and medical advances

The landscape of medicine is seeing a paradigm shift, with potentially effective novel cell-or tissue-based disease treatments emerging across a spectrum of diseases, including but not limited to cancers and degenerative diseases. Many rare diseases that currently lack effective therapeutic options are seeing the advent of potentially new targeted treatments such as disease-modifying drugs and gene editing[2].

The first successful uses of stem cells in medicine were developed empirically in the context of bone marrow transplantation, which involves reconstituting the blood and immune system with transplantation of haematopoietic stem cells (HSCs). Over the past 50 years, there has been increasing basic and translational research into the use of HSCs and other types of stem cells for a widening spectrum of potential clinical applications, including applications in tissue and cellular regeneration. Such work typically involves either somatic stem cells collected from adult or foetal tissues or pluripotent stem cells which are used to derive differentiated, somatic cell types used for therapy. Pluripotent stem cells can be derived either by culturing cells from early embryos at the blastocyst stage (embryonic stem cells) or through reprogramming of differentiated cells using combinations of transcription factors (induced pluripotent stem cells). Sources of cells may be allogeneic (from a donor other than the patient) or autologous (collected from the patient's own tissue).

The recognition of the central and pivotal role played by the immune system in many diseases, including cancer, has resulted in the development of novel and efficacious immune-cell-based therapies, such as chimeric antigen receptor modified T cells (CAR-T). Rigorous research leading to well-executed clinical trials has resulted in the demonstration of a therapeutic benefit of this technology in leukaemia and lymphoma[3]. However, there is a progressive understanding of the potential side effects of CAR-T based therapies, which can be common, and which have in some cases resulted in death directly linked to the administration of these cells[3].

After a rigorous evaluation of safety and efficacy data, the U.S. Food and Drug Administration approved products utilizing CAR-T technology for some relapsed and resistant blood cancers. Subsequently CAR-T cell products have also been approved in other regions, including the European Union, Japan and Australia.

The pathway to market authorization and entry into standard clinical practice followed by these CAR-T cell developers, which involved objective and rigorous assessment of the relative risks and benefits leading to regulatory approval and licensing, can serve as an

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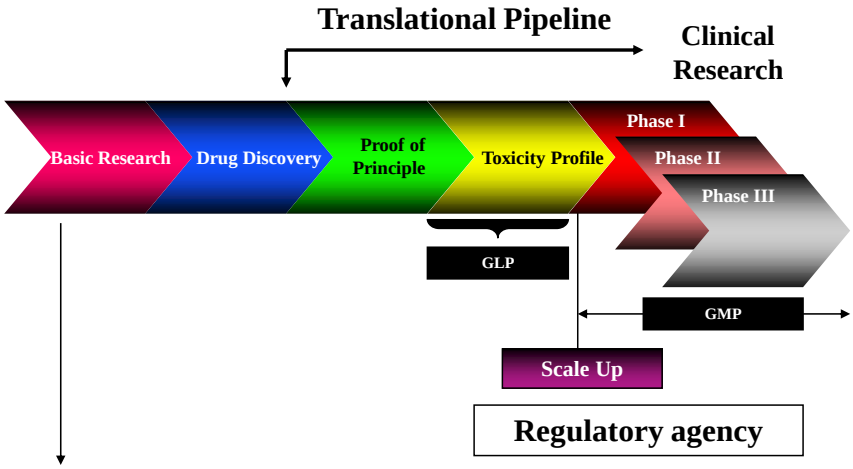
[2]Esrick EB, Bauer DE. Genetic therapies for sickle cell disease. *SeminHematol.* 2018;55(2):76-86.
[3]Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med.* 2018;378(5):439-48.

example for other cell-based therapeutics. The successful commercialization of CAR-T highlights the complex issues involving transfer of technologies and commercialization.

Some stem cell-based therapies show promise in the treatment of degenerative diseases, some of which have no effective therapeutic intervention. However promising this field may be, for the great majority of stem cell-based interventions currently being marketed directly to consumers, there is neither demonstration of proof of principle nor adequate understanding of potential side effects; both are needed to justify exploration of an intervention prior to establishment of efficacy and subsequent adoption into standard practice. These stem cell-based approaches require rigorous clinical studies that are necessary to demonstrate safety and efficacy[4]. Until adequate efficacy is demonstrated with no major safety concerns, licensing and regulatory approval leading to routine clinical use of these complex and speculative cell-based interventions have rightly not been granted in most jurisdictions. The direct marketing of unproven and unapproved interventions to consumers represents a risk for patients and for the entire cell therapy community.

Development of novel cell-based therapeutics

The general strategy in the development of a novel cellular therapeutics shown in Figure 1.



Typically, a new potential cellular therapy, emanating from discoveries in a basic research laboratory, is first tested for 'proof of concept' in relevant in vitro and in vivo model systems and other appropriate models for cell distribution and toxicology. With sufficient preclinical data demonstrating safety and efficacy in relevant animal models, large-scale product manufacturing schemes are developed, and production methods are tested. After current Good

[4]Hashimoto H, Olson EN, Bassel-Duby R. Therapeutic approaches for cardiac regeneration and repair. Nat Rev Cardiol. 2018;15(10):585-600.

Manufacturing Practice (cGMP) manufacturing methods are validated, the clinical trial can be initiated. Although straightforward by description, this strategy requires expertise in several diverse disciplines, including various specialties in medicine, basic and applied science, technology, quality assurance and regulatory affairs.

What is meant by “proven” and “unproven” in medicine?

Potential therapeutic treatments come with possible side effects. Clinical trials are designed to determine whether the measurable benefits of a product justify its measurable risks. We emphasize that "proof" in medicine does not imply either complete efficacy or safety, but rather that a given intervention has been through a rigorous process of analysis in clinical research and translational clinical studies that show that the intervention generally provides more benefit than risk for patients with specific clinical indications, leading to regulatory approval and adoption into standard use. Until this is achieved, a therapeutic treatment should be considered as “unproven” and should be subject to further investigation. The efficacy and safety profiles of any therapeutic can be more or less robustly established depending on the number, design, and size of published studies, as well as the cumulative clinical experience gathered with post-marketing evaluations; evidence-based medicine takes these factors into account.

Social media and internet-based worldwide communications can contribute to blurring the boundary between “proven” and “unproven” therapies for patient communities. The difference may be even more difficult to perceive for individuals who are affected by a life-threatening disease or a debilitating condition.

“Unproven cell-based therapies” are therefore those for which:

- Efficacy has yet to be established
- Risk-benefit profiles have not been adequately characterized
- Current standard of care and established treatment pathways have not been established
- Manufacturing has not been standardized based on adherence to mandatory guidelines
- Supervision, review and approval by competent government and/or professional organizations is lacking

Table 1 below,[5]summarizes these and others features on the definition of unproven cell-based therapies.

Table 1. Defining unproven cell-based therapies

✓	unclear scientific rationale to suggest potential efficacy
✓	lack of understanding on the mechanism of action and/or the biological function to support clinical use
✓	insufficient data from in vitro assays, animal models, and clinical studies regarding the safety profile to support the use in patients
✓	lack of a standardized approach to confirm product quality and ensure consistency in cell manufacturing
✓	inadequate information disclosed to patients to enable proper informed consent
✓	use within non-standardized or non-validated administration methods
✓	uncontrolled experimental procedures in humans

Crucially, "unproven" does not necessarily mean it would be ineffective, it means that sufficient data is currently lacking to prove effectiveness. Conversely "proven" does not imply without risk but that sufficient work has been done to understand the side effects of the therapy. Additionally, as is the case for blood transfusion, there should be recommendations and requirements regarding the institutional settings in which it is safe to deliver these complex cell-based therapies, as well as licensing of the manufacture of such products.

Risks

The scale of potential problems with unproven cell-based therapies is likely to be underestimated as treatments have been performed in unauthorized "clinics" that might not track or report adverse outcomes and might use ill-characterized products. Although the risks and toxicities of some cell-based therapies such as HSCs and CAR-T are progressively being recognized and appropriately managed, risks and toxicities of other cell-based therapies are incompletely understood.

Patients may not fully appreciate or report potential adverse outcomes, as these may not be adequately covered in the consent forms delivered to patients in the unproven cell therapy industry[6]. Clinically, due to lack of rigorous data, the nature and extent of acute or chronic

[5]Srivastava A, Mason C, Wagena E, Cuende N, Weiss DJ, Horwitz EM, Dominici M. Part 1: Defining unproven cellular therapies. *Cytotherapy*. 2016;18(1):117-9.

[6]Sugarman J, Barker RA. A Professional Standard for Informed Consent for Stem Cell Therapies. *JAMA*. 2019;322(17):1651-1652

adverse effects from the administration of complex and speculative cell-based products are still not fully understood. This has led to unexpected serious adverse, often life-threatening adverse effects such as the development of a neural glioproliferative tumour post intrathecal injections of putative foetal and post-natal stem cells, or vision loss after intravitreal injection of autologous "stem cells"[7,8].

Current status of unproven cell-based therapies

Aside from the robustness of data for haematopoietic stem cell transplants and CAR-T therapies, the current lack of substantial evidence of safety and efficacy for most other cell-based interventions has meant that it has still to meet the standards to justify either regulatory approval for marketing as medical products, or adoption as standard-of-care in medical practice. Encouragingly though, recent years has seen a substantial rise in the number of cell-based therapies being investigated in formal clinical trials.

This striking lack of evidence notwithstanding, an explosive international growth in the number of businesses engaged in the direct-to-consumer marketing of stem cell-based interventions has occurred. It has to be considered that few if any of the clinics delivering cells with unproven approaches seek regulatory approval through conventional national and international authorities. Some may also attempt to provide an impression of external approval through unrecognized certifications, clinical and scientific data published in journals with limited reputation and peer-review process and supposed patient testimonials distributed on well-designed websites and social media.

One 2016 global survey[9] identified over 400 websites advertising unproven uses of stem cells. A separate study[10] the same year found 341 businesses, associated with 570 partner clinics, in the United States alone. The number of such businesses also continues to grow worldwide, as

[7]Berkowitz AL, Miller MB, Mir SA, Cagney D, Chavakula V, Guleria I, et al. Glioproliferative Lesion of the Spinal Cord as a Complication of "Stem-Cell Tourism". *N Engl J Med.* 2016;375(2):196-8.

[8]Kuriyan AE, Albini TA, Townsend JH, Rodriguez M, Pandya HK, Leonard RE, 2nd, et al. Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD. *N Engl J Med.* 2017;376(11):1047-53.

[9]Berger I, Ahmad A, Bansal A, Kapoor T, Sipp D, Rasko JEJ. Global Distribution of Businesses Marketing Stem Cell-Based Interventions. *Cell Stem Cell.* 2016;19(2):158-62.

[10]Turner L, Knoepfler P. Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry. *Cell Stem Cell.* 2016;19(2):154-7.

reflected in recent national surveys from Japan[11], India[12] and Australia[13].The industry remains highly fluid and accurate numbers are not yet available for certain regions of the world, or for businesses that advertise in languages other than English. However, it is clear that the number of businesses engaged in this activity continues to grow rapidly around the world.

Such businesses frequently advertise "stem cell" treatments for an extraordinary range of serious medical conditions including autism, spinal cord injury, chronic heart failure, and numerous neurodegenerative diseases. Many marketers specifically target families of paediatric patients. Many use sophisticated online marketing strategies both to persuade prospective patients and to minimize their legal risks. In recent years, businesses often direct prospective patients to finance their treatments through medical loans or online crowdfunding campaigns[14].
The hype surrounding scientific breakthroughs in the field of stem cell biology is often oversold via the media, leading to false perceptions of efficacy and hope. This is in part understandable because current treatment options may not be available for many diseases. It is tantalizing to imagine that neural and functional recovery could be restored after stroke, or that damaged myocardial function in progressive incurable cardiomyopathy could be improved. It is unsurprising that members of the public are willing to seek out and pay for unproven stem cell therapies that claim to offer the chance of benefit by patients with incurable diseases.

Unique nature and manufacture of cell-based medicines

There are considerable differences between cell-based medicines, and in particular autologous products (i.e. CAR-T), and other biotechnologies and pharmaceutical drugs (including monoclonal antibodies or recombinant human factors). This is outlined in Table 2.

[11]Fujita M, Hatta T, Ozeki R, Akabayashi A. The current status of clinics providing private practice cell therapy in Japan. *Regen Med*. 2016;11(1):23-32.

[12]Tiwari SS, Desai PN. Unproven Stem Cell Therapies in India: Regulatory Challenges and Proposed Paths Forward. *Cell Stem Cell.* 2018;23(5):649-52.

[13] Lysaght T, Hendl T, Tan HL, Kerridge I, Stewart C. Open for business: a comparative study of websites selling autologous stem cells in Australia and Japan. *Regenerative Medicine*. 2017: 657-668
[14]Snyder J, Turner L, Crooks VA. Crowdfunding for Unproven Stem Cell-Based Interventions. JAMA. 2018;319(18):1935-6.

Table 2: Distinctions between biotechnology and cell therapy

	Biotechnology	Cell Therapy
Product	Cultured cells generate product	Living cells are product
Raw material	Seed cell lines	Unique, primary tissue
Variability, Heterogeneity	Limited	Substantial
Product definition	Well-defined products	Product defined through trials; Full definition may not be attainable
Process, Testing	Established early	Evolve through trials
Process Scale	Bulk processes predominate	Patient-specific products common

Due to these essentially differing characteristics, the following are key considerations for the testing, use and regulation of cell-based products:

1. Screening of donor prior to cell procurement.
2. Sterility and microbiological safety from the original tissue source and during processing and manipulation remain paramount in view of the "living" nature of these cell -based products.
3. Unlike the case for most pharmaceutical drugs, it has been possible for individuals treating patients to "directly produce and manufacture" some cell-based medicines, in some cases at the point of clinical care and "local" cell processing facilities. These include HSCs collected via blood draws or bone marrow aspiration and adipose-derived cells collected by liposuction, minimally processed, and re-grafted into the same patient. Certain blood products such as platelet-rich plasma (PRP) can be prepared easily using point-of-care devices.
4. Unlike the uniformity and purity attainable by modern pharmaceuticals, cell-based products inherently exhibit heterogeneity. Thus, criteria for determining medicinal product identity and characteristics, including measures of potency, mechanism of action, and consistency must paradoxically be both stringent and tolerant of the specific properties of the product. Conventional standards for mass manufacturing akin to pharmaceuticals are currently difficult to apply. This can result in relatively high costs, prevent testing on representative samples, and frequently allows for medical use of out-of-specification products.
5. Blood transfusion is an example of a cell-based medicine, which has been used in clinical practice for more than a century. It is life saving and an essential component of all health care systems. The accepted recommended practice of clinical blood transfusion remains hospital-based and manufacture is performed by licensed and authorized blood establishments. WHO has spent considerable effort in ensuring not only equitable access for all universally, but that the entire process—from donation to

infectious disease testing is tightly controlled to ensure safety and minimize transmission of pathogens? Aide-mémoires and guidelines for national systems have been initiated by WHO for this purpose to enforce quality, safety, and efficacy. A similar supportive guidance may be utilized and enforced for other types of cell-based therapies.

International Regulatory Landscape

Many countries and regions including the European Union, the United States, The People's Republic of China, Canada, and South Korea regulate human cell-based therapeutics nearly exclusively as medical products requiring premarket testing and approval. A few countries, such as Japan and Australia, have specific dual pathways that treat some cell-based therapeutics as regulated medical products and others as medical procedures which are regulated by a different pathway besides the national drug approval laws. It should be noted that the majority of nations have yet to establish specific laws or regulations on the development and clinical use of stem cell-based therapeutics.

The regulation of cell-based products typically involves a number of criteria for determining whether a given product will be considered a biologic drug. These include the extent to which the cells are manipulated prior to transplantation, whether they are intended for a use that is identical to their ordinary physiological function ("homologous use"), and whether they are expected to have systemic or metabolic effects. In some countries, cells from allogeneic sources are regulated separately from autologous cells. Likewise, some nations exempt certain cell types (e.g. blood, gametes) from their cell biologics regulatory frameworks. Additionally, some nations, such as Japan, have established accelerated pathways specifically for human cell-based products intended for use in regenerative medicine.

The lack of a fixed, global and harmonized regulatory framework creates a situation that is confusing for scientists, healthcare professionals and industry, and presumably even more so for the public. In this critical regard, WHO may represent a unifying body to encourage, coordinate and generate better worldwide harmonization.

Global marketing of unproven cell-based interventions: A problematic industry

In addition to the lack of robust evidence of safety and efficacy data that is required to justify routine commercial use of cell-based therapies, there are a number of highly problematic

features of the direct-to-consumer marketing of unproven cell interventions[15]. As noted above, reports of severe adverse events associated either with the harvesting or delivery of cells have been on the rise, including incidents of blindness, paralysis, stroke, and death[16]. Moreover, the lack of regulatory oversight in manufacturing and processing means that it is often unclear how the cells used in interventions of unknown safety and efficacy are obtained and processed. It is unclear as to exactly what cells are being administered, typically by systemic infusion or local injection, and whether the cells are even alive. Aside from physical risks, there are also considerable financial and psychological impacts. Misinformation about the current state of scientific evidence for cell-based therapies, in particular stem cells, may lead to confusion or mistrust of legitimate scientific and medical enterprises among members of the public, potentially damaging a promising field.

Despite existing regulatory frameworks in some countries, businesses marketing unproven cellular interventions have continued to operate with relative impunity. In the past, many such businesses were based in countries lacking clear regulations over cellular therapeutics and sought to attract international medical travellers by offering interventions unavailable in their home countries. However, the majority of cell marketing businesses now operate within the United States, Japan, Europe and other nations with well-established legal frameworks. This is attributable to a combination of factors. Drug regulatory agencies are insufficiently resourced to conduct effective monitoring, inspection, and enforcement actions. Ambiguities in relevant laws have been interpreted by businesses as effectively permissive. In some countries, for example, the manufacture of cell biologics is licensed by governments but not the indication for their use.

One example of this is the "same-surgical procedure" exemption in the U.S. federal regulations. Many marketers insisted that by collecting, processing, and re-implanting cells from the patient, typically harvested from either fat or bone marrow on an outpatient basis, they were exempt from federal oversight. In 2017, the US Food and Drug Administration (FDA) issued a final guidance document[17], which clarified that it interprets this exemption narrowly, as limited only to sizing, shaping, rinsing, and cleansing of an autologous human cellular product. European regulators have tightened this loophole by stating unambiguously that advanced therapy

[15] Lysaght, T., Lipworth, W, Hendl, T., Kerridge, I., Lee, T.L., Munsie, M., Waldby, C., and Stewart, C. The deadly business of an unregulated global stem cell industry. *Journal of Med Ethics.* 2017:744-746

[16] Bauer G, Elsallab M, Abou-El-Enein M. A Comprehensive Analysis of Reported Adverse Events in Patients Receiving Unproven Stem Cell-Based Interventions. *Stem cells Translational Medicine.* 2018:676-685

[17] US Food and Drug Administration. "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception: Guidance for Industry." Available at:https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf

medicinal products (ATMPs) manufactured and applied during the same surgical procedure are not exempted from the ATMP Regulation (including therefore GMP compliance)[18].

A second self-protective strategy employed by businesses marketing cells, and again in particular for stem cells, is in the claims and implications they make on their websites and social media, which often over-represent the likelihood of clinical benefit, under-represent the risks of cell harvesting and infusion or injection, and use language in ways designed to minimize accountability and exploit patients 'vulnerability. A typical feature of direct-to-consumer marketing of unproven stem cell interventions involves the use of "tokens of legitimacy,"[19] in which businesses make assertions about research publications (a phenomenon exacerbated by predatory/vanity publishers), patent applications, membership in professional organizations, collaborations with academic or industry, government accreditations intended to create an impression of scientific credibility. A particularly concerning form of this practice is the registration of open-label "research studies" on government online registries, such as clinicaltrials.gov, in which patients are required to pay in order ("pay-to-participate studies")[20] to enrol.

This profusion of "stem cell" clinics worldwide proclaiming unsubstantiated benefits are not only unethical and potentially dangerous but impedes the development of the field which depends on the unbiased and objective accumulation of data and clinical endpoints conducted in formal clinical studies.

Enabling factors

1. There is no consistent global regulatory approach overseeing an inherently complex and fast evolving landscape. Harmonized standards would help to reduce ambiguity and uncertainty and contribute to the creation of a common world market.
2. Many countries have yet to adopt regulations for stem cell-based interventions and in those that have, enforcement and interpretation of these regulations may be challenging.
3. There is a growing market for point-of-care devices that can be easily installed in individual clinics, for example devices for the collection and production of cell-based interventions, such as platelet-rich plasma (PRP) or adipose-derived cells to treat a variety of medical conditions with variable and often doubtful efficacy.

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[18] European Commission 2017. Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. Good Manufacturing Practice. Available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf

[19] Sipp D, Caulfield T, Kaye J, Barfoot J, Blackburn C, Chan S, et al. Marketing of unproven stem cell-based interventions: A call to action. *SciTransl Med.* 2017;9(397).

[20] Turner L. ClinicalTrials.gov, stem cells and 'pay-to-participate' clinical studies. *Regen. Med.*. 2017.

4. There is the perception that autologous cells are safe and therefore can be given without due oversight. In the context of the medical *prima facie* principle of "First, do no harm", relatively safe interventions without significant efficacy are still not justifiable.
5. There is considerable media hype and attention paid to the "unlimited potential" of stem cells with anecdotal reporting of "cures" from these stem cell therapies. As a result, there is corresponding public perception, reinforced by media hype, that stem cells are a panacea. The possibility of using autologous cells in some of these interventions makes it even more enticing.
6. These interventions are monetarily lucrative, catering not only to a domestic "market" but an increasing worldwide market of providers engaging in the promotion of "medical tourism" based on unproven cell interventions.
7. Some degenerative diseases (e.g. retinitis pigmentosa), rare diseases (e.g., muscular dystrophy) and forms of trauma (e.g., spinal cord injury) currently have no significant viable interventions or cure. The drive to seek experimental treatment is therefore understandable. However, it must be emphasized that for a medical experiment to be ethical, it must be designed and conducted in ways that enable the generation of valid data.
8. Pre-clinical and early clinical trial data suggest that some stem cell-based interventions have therapeutic potential. The field is progressing rapidly, and it is often difficult for the medical community to fully navigate and understand the benefits and risks of myriad cell-based interventions in different diseases. The situation is even more bewildering for the general public due to the abundance of online claims of almost magical cures and the difficulty in accessing and interpreting relevant patient information for a particular intervention in a specific disease.

Countermeasures to date and what needs undertaking:

Regulatory authorities have been cognizant of the situation but are hampered by a variety of reasons including unclear legislative guidance and insufficient staffing relative to the scale of the problem. The US FDA, Health Canada, and the Australian Therapeutic Goods Administration, among others, have responded recently with new guidance and increased resources committed to mitigate the rise of unproven products. Internationally, it remains urgent for governments and health authorities to act similarly, increase resources for enforcement, and achieve greater harmonization in terms of approach and regulatory frameworks.

International societies have also risen to the challenge by issuing clear, unambiguous published position statements and guidance papers[21,22].Leading this initiative, both the International Society for Stem Cell Research (ISSCR) and the International Society for Cell & Gene Therapy (ISCT) have taken an unequivocal stance on this "unregulated" practice.

Accreditation and certification schemes led by the main international societies such as those offered by AABB[23], FACT[24] and JACIE[25], can also offer reassurances to regulators and the public as to the quality of a center's organization and practices.
Centers should be reporting their activity to international registries such as CIBMTR[26] or EBMT[27]. The Registries in turn publish reports using data which gives overviews of the effectiveness of given therapies in terms of survival and mortality.

More international coordinated action is being taken and is critically needed. The Worldwide Network for Blood and Marrow Transplantation (WBMT) is in official relations with World Health Organization (WHO) and together with the spearheading initiatives of ISCT and the ISSCR, is aiming to tackle this issue head on by making clear that experimental therapies must be performed in a rigorous manner with robust clinical governance.

National/federal medical boards and federations are starting to implement punitive measures (warning, license suspensions) against those physicians who take the authority of their medical position in delivering unproven cell therapies.

ISSCR has also issued specific patient information that can be downloaded from their **Closer Look at Stem Cells** website (https://www.closerlookatstemcells.org/) providing guidance when considering stem cell based treatments. Work needs to be done to empower patient organizations and the public with adequate information about approved cell-based medicines and candidate therapies that are still in investigational trials[28].

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[21]Dominici M, Nichols K, Srivastava A, Weiss DJ, Eldridge P, Cuende N, et al. Positioning a Scientific Community on Unproven Cellular Therapies: The 2015 International Society for Cellular Therapy Perspective. *Cytotherapy*. 2015;17(12):1663-6.

[22]Sugarman J, Barker RA, Kerridge I, Lysaght T et al. Tackling Ethical Challenges of Premature Delivery of Stem Cell-Based Therapies. ISSCR 2018 Annual Meeting Focus Session Report. Stem Cell Reports.2018; (11):1021-25

[23]http://www.aabb.org/sa/Pages/default.aspx
[24]http://www.factwebsite.org/
[25]https://www.ebmt.org/jacie-accreditation
[26]https://www.cibmtr.org/Pages/index.aspx
[27]https://www.ebmt.org/ebmt-patient-registry
[28] International Society of Stem Cell Research 2019. Informed Consent Standard for Stem cell Based Interventions . Available at http://www.isscr.org/docs/default-source/policy-documents/isscr-informed-consent-standards-for-stem-cell-based-interventions.pdf

To this end, the ISCT has also coordinated an effort to list all approved cell-based products worldwide that have gained marketing authorization. This has been published and available as a free resource that will be updated continuously to reflect the current worldwide situation[1]. Appendix A provides a list of these approved products.

We should add that these different initiatives need greater integration. Patients, families, and caregivers should be educated to distinguish "proven" from "unproven" therapies. To this end, they should be advised to empower themselves with unbiased medical information so that they can critically distinguish hype from promise. Professional engagement of societies and charitable organizations supporting patients with specific diseases is also essential, as they are often central to patient advocacy and providing information and advice to patient communities across countries and languages.

Competent authorities together with professional associations and patient advocate groups should collectively disseminate information in a clear and comprehensible manner. Simultaneously, it is necessary that health care, regulatory, and legal authorities undertake consistent, appropriate and vigorous enforcement actions against marketers of unproven stem cells interventions, and that regulatory and legal frameworks be strengthened and harmonized. This will require international cooperation.

Key Issues and Recommendations for WHO

1. Acknowledge scale of the problem. This is a worldwide issue affecting all countries. It needs to be recognized and analysed.
2. Ensure that all countries strictly regulate the development and use of cell therapy products and avoid the over-inflated marketing of unproven cell-based therapies.
3. Recognize that international harmonization of regulations is required to support the development of evidence-based therapeutics and prevent clinics selling unproven cell-based therapies from moving among jurisdictions.
4. Regulators must invest in oversight to ensure compliance.
5. Recognize that cell and gene-based treatments show considerable promise, especially important in degenerative or rare diseases for which there may be a lack of effective therapies. Greater scientific understanding should be encouraged to assess the benefits and risks of cell-based interventions in order to accelerate the pathway from "unproven" to "proven" therapies for interventions that demonstrate promise.
6. Empower patients, families, and caregivers by providing evidence-based accurate information. Patient autonomy and freedom of choice are important but must be informed by accurate information and proper guidance from health care systems and the scientific and medical community. Professional engagement of societies and charitable organizations supporting patients with specific diseases is also essential, as

they are often central to patient advocacy and providing information and advice to patient communities across countries and languages.

7. Help establish and support systems to encourage rigorous assessment prior to marketing of treatments so that the benefits and risk/toxicity profiles can be objectively determined. To this end, cell-based interventions should be evaluated through clinical trials conducted at institutions with the appropriate infrastructure and organizational frameworks necessary to ensure ethical oversight and research trial governance. The evaluation of experimental cell-based interventions in such institutions will also allow for consistent, objective, and accurate reporting of clinical outcomes, adverse events, and facilitate large data set analysis.
8. Encourage responsible reporting and discourage deceptive advertising claims from clinics. Media reporting and marketing hyperbole has skewed public understanding and expectations surrounding cell-based therapeutics, especially with regard to stem cell interventions.
9. Reporting of adverse effects and toxicities associated with cell-based interventions should not only be encouraged but made imperative. Established hemovigilance systems for monitoring clinical blood transfusions and outcomes reporting of global registries serve as a successful example of safety reporting for both short term and longer-term safety and efficacy. Comparable short- and long-term safety monitoring should be extended to all cell-based interventions. One existing system is the NOTIFY Project, a joint global initiative, co-sponsored by the WHO with the Italian National Transplant Centre as its collaborating centre. NOTIFY promotes the governance of Medical Products of Human Origin (MPHO) in a manner that acknowledges their exceptional nature.
10. Encourage national and international societies to play an important role in highlighting this issue. WBMT, in official relations with WHO, will continue to work with WHO as a priority.
11. Encourage the take up of recognized accreditation and certification schemes by genuine healthcare providers in order to distinguish them from clinics with dubious practices.
12. Appreciate and not underestimate the impact of cell-based interventions on healthcare systems. These novel cell-based therapies may radically alter paradigms of care and treatment guidelines, such as in the use of CAR-T cells in leukaemia. The high cost and complexity of manufacture of some cell-based medicines are likely to impact equity of access. Urgent attention should be focused on achieving this equality including addressing the high pricing for approved products by pharmaceutical companies like CAR-Ts. Parallels again can be drawn with transfusion and transplantation, with both fields achieving greater global equity of access and improved quality over time due to efforts of the medical community and emphasis by WHO.

Overall, from the perspective of individual countries and national healthcare systems, there should be an emphasis on regulation, protection of their citizens, assessment of the impact on

existing healthcare costs, and the economic potential of these therapies as well as investment in such technologies for healthcare development.

From the clinical perspective of the medical and scientific professions, critically important issues like the acquisition of adequate knowledge and understanding of when to use a specific cell therapy, awareness of the side effect profile and unbiased interpretation of medical literature should be emphasized. There should also be an emphasis on the ethical issues of certain stem cell based and gene-edited therapies and an adherence to the primary principle of the practice of medicine: “First do no harm”.

From the patient/public perspective, there should be recognition of the potential availability of cell-based therapies for rare and/or degenerative diseases, tempered by the clear understanding that all therapies, cell-based or otherwise, must demonstrate a satisfactory risk/benefit profile prior to routine use in regular clinical practice outside of clinical trials. Patient associations and advocates can be instrumental in this process.

Concluding Statements and Next Steps

The purpose of this position paper is to report to WHO on the scale, importance and characteristics of the global cell-based industry with emphasis on unproven cell therapies currently being performed without adequate regulatory and ethical oversight. The situation is exacerbated by widespread direct-to-consumer marketing of such unproven cell-based interventions, in particular for stem cells.

The WBMT seeks to advise and support WHO in assisting Member States in establishing and enforcing national and/or regional regulations over the medical use of cell-based interventions, as well as in formulating clear recommendations and guidance documents endorsed by WHO. Strong and active international cooperation and harmonization is urgently required and WHO is ideally positioned to coordinate this.

The proposal following this report is a recommendation for WHO to convene a formal task force to examine all these issues in greater detail and to highlight this as an agenda item in the annual WHO General Assembly.

This position paper is consistent with the stance of all the societies represented, and with the aims of many national regulatory agencies.

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The members of this task force come from the following countries:

Australia, France, Germany, India, Italy, Japan, Paraguay, Saudi Arabia, Singapore, UK, and USA.

This position paper has been endorsed by the following international organizations with a global reach and an interest in cell based medicine:

Worldwide Network for Blood and Marrow Transplantation

American Association of Blood Banks (AABB) and the AABB Centre for Cellular Therapies

American Society for Transplantation and Cellular Therapy (ASTCT)

Asia-Pacific Blood and Marrow Transplantation Group (APBMT)

Asian Cellular Therapy Organization (ACTO)

Eastern Mediterranean Blood and Marrow Transplantation Group (EMBMT)

European Society for Blood and Marrow Transplantation (EBMT)

International Society for Blood Transfusion (ISBT)

International Society for Cell & Gene Therapy (ISCT)

International Society for Stem Cell Research (ISSCR)

Joint Accreditation Committee ISCT-Europe and EBMT (JACIE)

Latin American Bone Marrow Transplantation Group (LABMT)

World Marrow Donor Association (WMDA)

Acknowledgements for input

Hildegard Grenix-WBMT
Daniel Weisdorf-WBMT
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Lydia Foeken: WMDA
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Attached

Appendix A

Cytotherapy, 2018; 0001–13

International Society for Cellular Therapy
ISCT®

Cell, tissue and gene products with marketing authorization in 2018 worldwide

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Abstract

Cell and gene therapies (CGTs) are progressively entering into clinical practice in different parts of the world. The International Society for Cell & Gene Therapy (ISCT), a global scientific society, has been committed since 1992 to supporting and developing knowledge on clinical applications of CGTs. Considering the number of products that have been progressively approved and, in some cases, withdrawn in recent years, the ISCT would like to present a brief annual report on CGTs with marketing authorization (MA) in different regions. This article reflects the dynamic momentum around authorized CGTs coinciding with the parallel increase of unproven approaches where cells are delivered without appropriate and rigorous scientific and regulatory assessment and authorization. This is intended to be a living document with a yearly update linked to a dedicated section of the ISCT website for faster adjustments. The aim is to ultimately inform, by periodic snapshots, the scientific community, healthcare stakeholders and patient associations on authorized CGT products as a way to increase communication around the approved therapeutic approaches charged with heightened expectations.

Introduction

The International Society for Cell & Gene Therapy (ISCT) is committed to translating cellular therapy into safe and effective treatments to improve patients' lives while minimizing and balancing risks for patients. Being aware that many unproven or insufficiently proven cell-based treatments are commercially available for hopeful individuals seeking cures or health improvement for a variety of conditions, the ISCT created the ISCT Presidential Task Force (PTF) on the Use of Unproven Cellular Therapies (UCT) in 2014. The PTF-UCT strives to characterize unproven cellular interventions and promote safe and effective practices worldwide [1,2].

In line with the above goals, the PTF-UCT has launched several initiatives including providing updated information on approved cellular therapies. For a list of PTF-UCT–authored resources visit http://www.celltherapysociety.org/page/UCT. In this document the PTF-UCT has summarized cell, tissue and gene medicinal products authorized for commercialization by regions/countries, to help patients seeking safe and effective treatments. We have not included any products that are categorized as medical devices, even if they are cell-based. If a patient lives in one of the regions/countries included in the document and a healthcare professional or a business is offering a cell-based treatment not listed, they should ask whether they are going to receive the treatment as part of a clinical trial. If not, the ISCT recommends asking for more information about the "regulatory status" of the treatment they are going to receive to make an informed decision.

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(Received 20 September 2018; accepted 24 September 2018)

https://doi.org/10.1016/j.jcyt.2018.09.010

Definitions and principles

Human cell– or tissue-based products are highly heterogeneous and regulatory authorities will always apply their rulings on a case-by-case basis. Nevertheless, at present, most of the cell- and tissue-based products are considered biological medicinal products in those countries with more developed regulatory structures. The development of safe and effective "proven" cell therapies requires testing these medicinal products according to some general principles [3]. Before administration into humans, both biological activity and toxicity of the investigational medicinal product must be tested in relevant animal model(s). Researchers must then seek approval of an institutional review board (IRB) for all centers involved in the clinical trial as well as an authorization from the national regulatory agencies of the countries where patients will be recruited, irrespective of their nationalities. The sponsor's duties also include ensuring: (i) that there is an insurance policy in place to cover any liability, (ii) that recruitment of subjects is done after appropriate informed consent and (iii) that medicinal product batches for release conform to specifications. If the regulatory bodies determine that quality, safety and efficacy of a cell- or tissue-based medicinal product are sufficiently established through successful clinical phases (clinical trial phase 1, 2 and 3), then the next step is to apply for marketing authorization (MA). After that, the company that holds the MA can commercialize the medicinal product in the countries in which the product has been granted MA. In some cases, MA is provisional and post-marketing surveillance studies are required. Of note, some countries permit exceptions to this authorization rule depending on the nature of the medicinal product, be it industrial or otherwise. In any case, the use of a medicinal product has to be supervised by a regulatory body.

Identified cell and gene therapies with MA

We have identified and listed cell and gene therapies (CGTs) with MA based on available information, considering as a source of trustworthy information the regulatory body web resources, official press release by the interested companies or other source of data as indicated in Tables I–X where countries/regions are listed in alphabetical order. The list has been updated as of September 15, 2018, unless otherwise specified.

In Figure 1, we present the distribution of authorized CGT products by region. In addition, we have listed (Table XI) the CGT approaches that have received a Regenerative Medicine Advanced Therapy (RMAT) designation by the United States Food and Drug Administration (USFDA) [4] but have not been approved as of September 2018. In Figure 2, we have categorized CGT products with MA worldwide in three different ways, namely, by product, therapy and disease type. Finally, in Figure 3 we present CGT products according to the year in which they received MA.

Several products are currently available in different regions but have the same MA holder (YESCARTA, KYMRIAH, IMLYGIC, RMS Ossron/OSSGROW and Chondron/CARTIGROW). These products are taken into account only once in Figures 2 and 3, leading to a total number of 44 unique products.

Discussion and conclusions

The goal of this article is to provide a quick reference for anyone interested in a snapshot, to be updated annually, of the CGT landscape worldwide. This list may not be exhaustive and additional CGT products with MA will be included in future updates. To our knowledge, no cell/tissue/gene products have been authorized for marketing in Brazil, Hong Kong, Israel, Malaysia, Singapore and Taiwan as of September 2018.

We have identified 44 unique products, 37 of them are cell and tissue therapies (84%) and mainly autologous (55%) (Figure 2). As far as targeted diseases are concerned, more than one third of the

Table I. List of cell/tissue/gene products with MA in Australia by TGA.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Chondrocytes - T - Ortho-ACI (Orthocell Pty Ltd)	Autologous cultured chondrocytes for use in treatment of cartilage lesions associated with the knee, patella and ankle	Cell therapy product	26-Mar-2017	Still in market	Click here for link to TGA website

TGA, Therapeutic Goods Administration.

Table II. List of cell/tissue/gene products with MA in Canada by Health Canada (March 2018).

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
KYMRIAH (NOVARTIS PHARMACEUTICALS CANADA INC)	CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of pediatric and young adult patients 3–25 y with B-cell ALL who are refractory, have relapsed after allogeneic SCT or are otherwise ineligible for SCT, or have experienced second or later relapse and for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma.	Gene therapy product	05-Sep-2018	In market	Click here for link to Health Canada website
Prochymal (MESOBLAST INTERNATIONAL SARL)	Allogeneic *ex vivo*–cultured adult human mesenchymal stromal cells for the management of aGvHD in pediatric patients	Cell therapy product	02-May-2015	The product was never marketed in Canada	Click here for link to Health Canada website

ALL, acute lymphoblastic leukemia; SCT, stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; aGVHD, acute graft-versus-host disease.

Table III. List of cell/tissue/gene products with MA in China by CSFDA.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Gendicine (Shenzhen SiBiono GeneTech Co. Ltd.)	Recombinant adenovirus expressing p53 for treatment of head and neck squamous cell carcinoma	Gene therapy product	Oct-2003	Still in market	Click here

CSFDA, Chinese Food and Drug Administation.

products are intended for the treatment of oncological or hematologic diseases.

As shown in Figure 3, the number of products with MA has increased in recent years. For example, those authorized from 2015 to September 2018 represent 45%. Unfortunately, there has been a parallel increase in the number of businesses offering unproven and unlicensed cell-based interventions [5,6].

Even though the distribution of authorized CGTs shows important differences among countries or regions, it is not our intention to debate the complex financial, societal and scientific reasons behind these differences or the impact of different regulatory systems on the number of marketed products. As members of the ISCT PTF-UCT, our main objective is to help patients make informed decisions before receiving a cell or gene treatment so that they can avoid being exposed to unproven and unlicensed cell interventions. For that purpose, we aim to provide a reliable, up-to-date resource where patients or professionals can check whether a cell or gene therapy has been approved by a regulatory/medicine agency.

As mentioned before, the ISCT recommends asking for information about the "regulatory status" of the treatment patients are going to receive to make

Table IV. List of Cell/Tissue/Gene Products with MA in Europe by EMA.

Name (MA holder)	Product description and indication(s)	ATMP	Date of MA	Current status	Additional information
YESCARTA (Kite Pharma EU B.V.)	CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory DLBCL and PMBCL, after two or more lines of systemic therapy	GTMP	23-Aug-2018	Details of MA conditions not displayed at EMA website as of 31-Aug-2018	Click here for link to EMA website
KYMRIAH (Novartis Europharm Limited)	CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of pediatric and young adult patients up to 25 y of age with B-cell ALL that is refractory, in relapse post-transplantation or in second or later relapse, and for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy	GTMP	27-Aug-2018	Details of MA conditions not displayed at EMA website as of 31-Aug-2018	Click here for link to EMA website
ALOFISEL (Takeda Pharma A/S)	Expanded allogeneic adipose stem cells as a suspension for injection for the treatment of complex perianal fistulas in patients with Crohn's disease	SCTMP	27-Mar-2018	The company will complete a study to continue to collect information on the effectiveness and safety	Click here for link to EMA website
SPHEROX (CO. DON AG)	Spheroids of human autologous matrix-associated chondrocytes for knee-repairing cartilage defects	TEP	10-Jul-2017	MA under several obligations (post-authorization long-term efficacy and safety study, prospective process validation study and re-validation of the potency assay)	Click here for link to EMA website
ZALMOXIS (MolMed SpA)	Donor's T lymphocytes genetically modified with a suicide gene as a control mechanism for GVHD after haploidentical bone marrow transplantation	GTMP	18-Aug-2016	Granted MA under conditional approval	Click here for link to EMA website
STRIMVELIS (GSK Trading Services Limited)	Autologous CD34+ cells transduced with a retroviral vector that encodes for the human ADA cDNA sequence for severe combined immunodeficiency due to ADA deficiency	GTMP	26-May-2016	Granted MA under additional monitoring until 2037	Click here for link to EMA website
IMLYGIC (Amgen Europe B.V.)	Oncolytic immunotherapy derived from a herpex simplex virus-1 genetically engineered to infect and replicate within melanoma cells and to produce GM-CSF for unresectable melanoma	GTMP	16-Dec-2015	Granted MA under additional monitoring	Click here for link to EMA website
HOLOCLAR (Chiesi Farmaceutici S.p.A.)	*Ex vivo*—expanded autologous human corneal epithelial cells containing stem cells for severe limbal stem cell deficiency	SCTMP	17-Feb-2015	Granted MA under conditional approval	Click here for link to EMA website

EMA, European Medicines Agency; ATMP, Advanced Therapy Medicinal Product; PMBCL, primary mediastinal large B-cell lymphoma; ADA, Adenosine deaminase; cDNA, complementary DNA; TEP, Tissue Engineered Product; GTMP, Gene Therapy Medicinal Product; SCTMP, Somatic Cell Therapy Medicinal Product; EC, European Commission.

Table V. List of cell/tissue/gene products with MA withdrawn or suspended in Europe by EMA.

Name (MA holder)	Product description and indication(s)	ATMP	Date of MA	Current status	Additional information
PROVENGE (Dendreon)	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor for metastatic prostate cancer	SCTMP	6-Sep-2013	Granted MA under additional monitoring. Withdrawn: company announced bankruptcy in 2015	Click here for link to EMA website
MACI (Aastrom Biosciences, Inc.)	Matrix applied characterized autologous cultured chondrocytes for repairing knee cartilage defects	TEP	27-Jun-2013	Granted MA under additional monitoring. MA suspended: 25-Sep-2014	Click here for link to EMA website
GLYBERA (uniQure biopharma BV)	Alipogene tiparvovec (human lipoprotein lipase gene variant in a adeno-associated viral vector) for adult patients with familiar lipoprotein lipase deficiency	GTMP	25-Oct-2012	Granted MA under additional monitoring. Withdrawn: MA expired on 25-Oct-2017. The company did not apply for renewal due to the lack of demand	Click here for link to EMA website
CHONDROCELECT (TiGenix NV)	Characterized viable autologous cartilage cells expanded *ex vivo* for repairing knee cartilage defects	TEP	5-Oct-2009	The product was reimbursed in 3 countries. Withdrawn: 30-Nov-2016. Requested by the company for commercial reasons	Click here for link to EMA website

Table VI. List of cell/tissue/gene products with MA in India by DCGI.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
CARTIGROW™ (Chondron ACI) (RMS Regrow)	Autologous cultured cartilage cells for treatment of articular cartilage defects	Cell therapy product	Apr-2017	Conditional approval, post-market surveillance study required (50 subjects)	Click here
OSSGROW™ (Ossron ABI) (RMS Regrow)	Autologous cultured osteoblasts for avascular necrosis of hip	Cell therapy product	Apr-2017	Conditional approval, post-market surveillance study required (50 subjects)	
APCEDEN (APAC Biotech)	Autologous monocyte-derived mature dendritic cells for treatment of prostate, ovarian, colorectal and non-small cell lung carcinoma	Cell therapy product	Mar-2017	Conditional approval, post-market surveillance study required	Click here
Stempeucel® (Stempeutics Research)	*Ex vivo*—cultured adult allogeneic mesenchymal stromal cells for treatment of critical limb ischemia due to Thromboangiitis Obliterans (Buerger's disease)	Cell therapy product	May-2016	In market, limited release (200 patients on a cost recovery basis), post-market surveillance study required	Click here

DCGI, Drug Controller General of India.

an informed decision. This is particularly relevant for patients living in one of the regions/countries included in the document who seek safe and effective treatments, should a healthcare professional or a business offer a CGT that is neither listed nor part of a clinical trial.

Acknowledgments

Authors are grateful to the entire PTF-UCT for the fruitful suggestions and to the ISCT Head Office in Vancouver, in particular to Iulia Dude and Sophie Bockhold, for the support in

Table VII. List of cell/tissue/gene products with MA in Japan by PMDA.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information (In Japanese)
Temcell HS (JCR Pharmaceuticals Co. Ltd.)	Allogeneic mesenchymal stromal cells for treatment of aGVHD	Cell therapy product	Sep-2015	In market	Click here for link to PMDA website
HeartSheet (Terumo Corporation, Ltd.)	Autologous skeletal myoblast sheet product for the treatment of severe heart failure	Tissue engineered product	Sep-2015	Conditional approval	Click here for link to PMDA website
JACC (J-TEC)	Autologous cultured cartilage	Tissue engineered product	Jul-2012	Still in market, previous authorization was as medical device	Click here for link to PMDA website
JACE (J-TEC)	Autologous cultured epidermis for treatment of severe burns	Tissue engineered product	Oct-2007	Still in market, previous authorization was as medical device	Click here for link to PMDA website

PMDA, Pharmaceuticals and Medical Devices Agency.

Table VIII. List of cell/tissue/gene products with MA in New Zealand by MEDSAFE.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Prochymal (Osiris Therapeutics Incorporated)	Allogeneic *ex vivo*–cultured adult human mesenchymal stromal cells indicated for the rescue of patients NLT 6 mo to 17 y of age with aGVHD, refractory to treatment with systemic corticosteroid therapy or other immunosuppressive agents	Cell therapy product	14-Jun-2012	Approval lapsed	Click here for link to MEDSAFE website

MEDSAFE, Medicines and Medical Devices Safety Authority; NLT, Not Lower Than.

Table IX. List of cell/tissue/gene products with MA in South Korea by MFDS.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
KeraHeal-Allo™ (Biosolution Co., Ltd.)	Composite cell product (allogeneic skin-derived keratinocytes suspended in a thermosensitive hydrogel) for deep 2nd degree burns	Cell therapy product	16-Oct-2015	Still in market	Click here for link to MFDS website
NEURONATA-R® (Corestem, Inc.)	Autologous bone marrow mesenchymal stromal cell therapy for Amyotrophic Lateral Sclerosis	Cell therapy product	30-Jul-2014	Orphan product	Click here for link to MFDS website
Cupistem® (Anterogen)	Autologous adipose tissue–derived mesenchymal stromal cell for Crohn's fistula	Cell therapy product	18-Jan-2012	Covered by insurance as of Jan-2014, orphan product	Click here for link to MFDS website
CARTISTEM® (Medipost Co., Ltd.)	Human umbilical cord blood–derived mesenchymal stromal cells for the treatment of knee articular cartilage defects in patients with osteoarthritis (ICRS grade IV)	Cell therapy product	18-Jan-2012	Still in market	Click here for link to MFDS website

(*continued*)

Table IX. (*Continued*).

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Cellgram®-AMI (Pharmicell Co., Ltd.)	Autologous bone barrow–derived mesenchymal stromal cells for acute myocardial infarction patients (improvement of LVEF)	Cell therapy product	1-Jul-2011	Name at time of approval was Heart-icellgram®-AMI, still in market	Click here for link to MFDS website
CureSkin Inj. (S. Biomedics Co., Ltd.)	Autologous dermal fibroblasts (depressed acne scar)	Cell therapy product	11-May-2010	Still in market	Click here for link to MFDS website
Queencell® (Anterogen)	Autologous adipose tissue–derived adipose cell by minimal manipulation for subcutaneous tissue defect	Cell therapy product	26-Mar-2010	Still in market	Click here for link to MFDS website
Kaloderm® (Tego Science, Inc)	Allogeneic keratinocytes (cell sheet) for deep 2nd degree burn or diabetic foot ulcer	Tissue engineered product	21-Mar-2005 (2nd degree burn) 24-Jun-2010 (Diabetic foot ulcer)	Still in market	Click here for link to MFDS website
RMS OssronTM (Sewon Cellontech Co., Ltd.)	Cultured autologous osteoblasts for focal bone formation, can be used with or without fibrin glue	Cell therapy product	26-Aug-2009	Still in market	Click here for link to MFDS website
Immuncell-LC (GC Cell Corp.)	Autologous activated T cell for liver cancer (hepatocellular carcinoma)	Cell therapy product	6-Aug-2007	Currently in market for hepatocellular carcinoma and in clinical trials for newly diagnosed glioblastoma (phase 3, completed) advanced pancreatic cancer (phase 2, completed)	Click here for link to MFDS website
CreaVax-RCC® (JW CreaGene Corporation)	Autologous dendritic cells for metastatic renal cell carcinoma	Cell therapy product	15-May-2007	Received tentative approval in 2007 and product manufacture license as export product in 2013 from MFDS	Click here for link to MFDS website
KeraHeal® (Biosolution Co., Ltd.)	Autologous skin-derived keratinocytes for deep 2nd degree burns that cover >30% of TBSA and 3rd degree burns that cover >10% of TBSA	Cell therapy product	3-May-2006	Still in market	Click here for link to MFDS website
Holoderm® (Tego Science, Inc)	Autologous keratinocytes for deep 2nd degree burns that cover >30% of TBSA and 3rd degree burns that cover >10% of TBSA	Tissue engineered product	10-Dec-2002	Still in market, reimbursed by insurance	Click here for link to MFDS website
ChondronTM (Sewon Cellontech Co., Ltd.)	Cultured autologous chondrocytes for focal cartilage defect of knee, can be used with or without fibrin glue	Cell therapy product	30-Jan-2001	Still in market	Click here for link to MFDS website

MFDS, Ministry of Food and Drug Safety; ICRS, International Cartilage Regeneration & Joint Preservation Society; LVEF, left ventricular ejection fraction; TBSA, Total Burn Surface Area.

Table X. List of cell/tissue/gene products with MA in the United States by USFDA.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
HPC, Cord Blood (MD Anderson Cord Blood Bank)	For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired or result from myeloablative treatment	Cell therapy product	06-Jun-2018	Still in market	Click here for link to FDA website
LUXTURNA (voretigene neparvovec-rzyl) (Spark Therapeutics, Inc.)	Adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy	Gene therapy product	19-Dec-2017	Still in market	Click here for link to FDA website
YESCARTA (axicabtagene ciloleucel) (Kite Pharma, Incorporated)	A CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma	Gene therapy product	18-Oct-2017	Still in market	Click here for link to FDA website
KYMRIAH (tisagenlecleucel) (Novartis Pharmaceuticals Corporation)	CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of patients up to 25 y of age with B-cell precursor ALL that is refractory or in second or later relapse	Gene therapy product	30-Aug-2017	Still in market	Click here for link to FDA website
MACI (Vericel Corporation)	Autologous cultured chondrocytes on a porcine collagen membrane for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults	Tissue engineered product	13-Dec-2016	Still in market	Click here for link to FDA website
Clevecord (HPC, Cord Blood) (Cleveland Cord Blood Center)	For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired or result from myeloablative treatment	Cell therapy product	1-Sep-2016	Still in market	Click here for link to FDA website
HPC, Cord Blood (Bloodworks)	For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired or result from myeloablative treatment	Cell therapy product	28-Jan-2016	Still in market	Click here for link to FDA website
IMLYGIC (talimogene laherparepvec) (Amgen Inc.)	Genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery	Gene therapy product	27-Oct-2015	Still in market	Click here for link to FDA website
HPC, Cord Blood (LifeSouth	For use in unrelated donor hematopoietic progenitor cell transplantation	Cell therapy product	13-Jun-2013	Still in market	

(*continued*)

Table X. (*Continued*).

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Community Blood Centers, Inc.)	procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired or result from myeloablative treatment				Click here for link to FDA website
ALLOCORD (SSM Cardinal Glennon Children's Medical Center)	For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired or result from myeloablative treatment	Cell therapy product	30-May-2013	Still in market	Click here for link to FDA website
Ducord (HPC, Cord Blood) (Duke University School of Medicine)	For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired or result from myeloablative treatment	Cell therapy product	4-Oct-2012	Still in market	Click here for link to FDA website
HPC, Cord Blood (Clinimmune Labs, University of Colorado Cord Blood Bank)	For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired or result from myeloablative treatment	Cell therapy product	24-May-2012	Still in market	Click here for link to FDA website
GINTUIT (Organogenesis, Inc.)	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen (cellular sheets) for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults	Tissue engineered product	9-Mar-2012	Still in market	Click here for link to FDA website
Hemacord (HPC, Cord Blood) (New York Blood Center, Inc.)	For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired or result from myeloablative treatment	Cell therapy product	1-Nov-2011	Still in market	Click here for link to FDA website
Laviv® (Azficel-T) (Fibrocell Technologies, Inc.)	Autologous fibroblasts for improvement of the appearance of moderate-to-severe nasolabial fold wrinkles in adults	Cell therapy product	21-Jun-2011	Still in market	Click here for link to FDA website
PROVENGE (sipuleucel-T) (Dendreon Corporation)	Autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer	Cell therapy product	29-Apr-2010	Still in market	Click here for link to FDA website

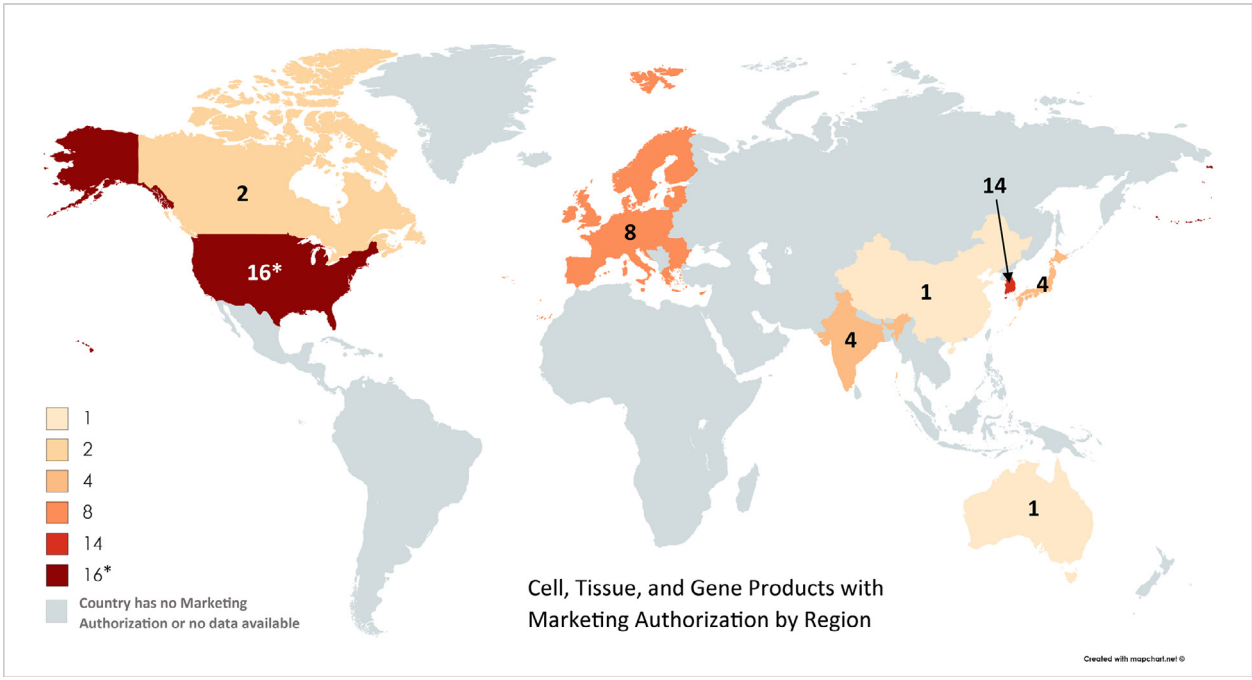

Figure 1. Number of cell, tissue and gene products with MA per region. *Eight products based on cord blood hematopoietic progenitors for unrelated donor hematopoietic progenitor cell transplantation have been included in the US's total number. These hold a MA license only in the US. Similar products are available in most countries as cell transplants and not as marketed products. The number of products presented in this figure does not include either products with Regenerative Medicine Advanced Therapy (RMAT) designation (United States Food and Drug Administration [USFDA]) or products with suspended MA.

Table XI. List of cell/tissue/gene products with RMAT Designation [4] in the United States by USFDA (Sep-2018).

Name (MA holder)	Product description and indication (s)	Product category	Date of RMAT designation	Additional designations	Additional information
AT132 (Audentes Therapeutics, Inc.)	AAV-mediated gene therapy for the treatment of XLMTM, a rare monogenic disease caused by mutations in the MTM1 gene	Gene therapy product	21-Aug-2018	Rare pediatric disease; fast track; orphan drug	Press release
Romyelocel-L (Cellerant Therapeutics, Inc.)	Off-the-shelf human myeloid progenitor cells for the prevention of serious bacterial and fungal infections in patients with *de novo* AML undergoing induction chemotherapy	Cell therapy product	02-Jul-2018		Press release
VY-AADC (Voyager Therapeutics, Inc.)	AAV-mediated gene therapy for the treatment of Parkinson's disease in patients with motor fluctuations that are refractory to medical management	Gene therapy product	21-Jun-2018		Press release
CLBS14-RfA (Caladrius Biosciences, Inc.)	CD34+ cell therapy program for the treatment of refractory angina	Cell therapy product	19-Jun-2018		Press release
NSR-REP1 (Nightstar Therapeutics plc)	AAV-mediated gene therapy for the treatment of choroideremia, a rare, degenerative, genetic retinal disorder that leads to blindness	Gene therapy product	14-Jun-2018		Press release
ABO-102 (Abeona Therapeutics Inc.)	AAV-mediated gene therapy for the treatment of Sanfilippo syndrome Type A (MPS IIIA), a rare autosomal-recessive lysosomal storage disease	Gene therapy product	23-Apr-2018		Press release

(*continued*)

Table XI. (*Continued*).

Name (MA holder)	Product description and indication (s)	Product category	Date of RMAT designation	Additional designations	Additional information
AmnioFix® (MiMedx)	Allogeneic micronized dehydrated human amnion/chorion membrane for use in the treatment of OA of the knee	Tissue engineered product	9-Mar-2018		Press release
CAP-1002 (Capricor Therapeutics)	Allogeneic cell therapy (cardiosphere-derived cells) that is currently in clinical development for the treatment of Duchenne muscular dystrophy	Cell therapy product	5-Feb-2018	Orphan drug; rare pediatric disease	Press release
EB-101 (Abeona Therapeutics Inc.)	Gene-corrected autologous cell therapy product for patients with RDEB	Gene therapy product	29-Jan-2018	Breakthrough therapy; orphan drug; rare pediatric disease	Press release
MPC therapy (Mesoblast Limited)	MPC therapy in the treatment of patients with heart failure with left ventricular systolic dysfunction and LVADs	Cell therapy product	21-Dec-2017		Press release
CEVA101 (Cellvation)	Autologous bone marrow–derived stem cells for the treatment of traumatic brain injury	Cell therapy product	8-Nov-2017		Press release
Multistem (Athersys)	Proprietary stem cell product for the treatment of ischemic stroke	Cell therapy product	5-Oct-2017		Press release
AST-OPC1 (Asterias Biotherapeutics)	Oligodendrocyte progenitor cells manufactured from pluripotent embryonic stem cells for treatment of patients with spinal cord injury	Cell therapy product	2-Oct-2017		Press release
LentiGlobin® BB305 (Bluebird Bio)	*Ex vivo* modified autologous hematopoietic stem cells for treatment of transfusion-dependent β-thalassemia (also known as β-thalassemia major) and severe SCD	Gene therapy product	1-Oct-2017		Press release
ATIR101™ (Kiadis Pharma)	Adjunctive immunotherapeutic on top of allogeneic HSCT	Cell therapy product	20-Sep-2017		Press release
StrataGraft (Mallinckrodt plc)	Autologous skin cell product for the treatment of deep partial thickness burns	Tissue engineered product	18-Jul-2017		Press release
Ixmyelocel-T (Vericel)	Autologous expanded multicellular (mesenchymal cells, monocytes and alternatively activated macrophages) product for the treatment of patients with advanced heart failure due to ischemic dilated cardiomyopathy	Cell therapy product	10-May-2017		Press release
jCell (jCyte)	Adult retinal progenitor cells for the treatment of RP	Cell therapy product	2-May-2017		Press release
RVT-802 (Enzyvant)	Allogeneic thymic tissue for the treatment of primary immune deficiency resulting from cDGS	Cell therapy product	17-Apr-2017	Breakthrough therapy, rare pediatric disease, orphan drug	Press release
HUMACYL® (Humacyte)	HAV for patients undergoing hemodialysis	Tissue engineered product	20-Mar-2017		Press release
JCAR017 (Juno Therapeutics)	Treatment of r/r aggressive large B-cell non-Hodgkin lymphoma	Cell therapy product			

AAV, adeno-associated virus; XLMTM, X-linked Myotubular Myopathy; AML, acute myeloid leukemia; OA, osteoarthritis; RDEB, recessive dystrophic epidermolysis bullosa; MPC, mesenchymal precursor cell; LVADs, left ventricular assist devices; SCD, sickle cell disease; HSCT, hematopoietic stem cell transplantation; RP, retinitis pigmentosa; cDGS, complete diGeorge Syndrome; HAV, human acellular vessel.

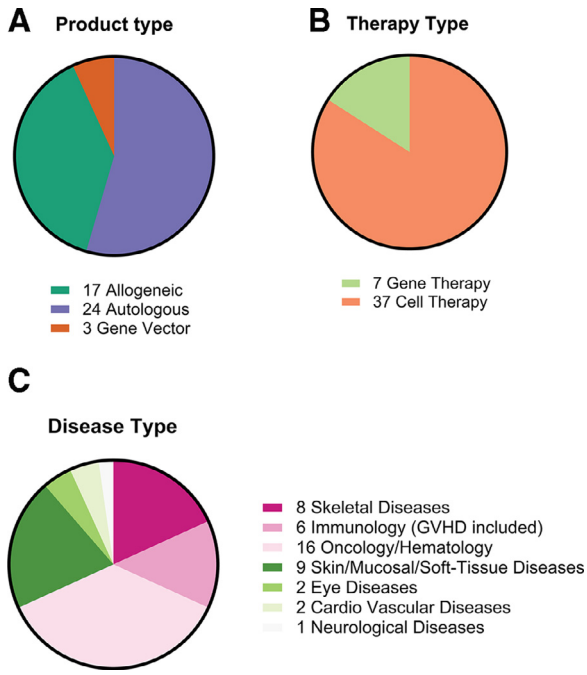

Figure 2. Cell, tissue and gene products with MA worldwide (44 unique products) organized by (A) product type, (B) therapy type and (C) disease type. "Cell Therapy" products in (B) also include tissue engineered products. Eight products based on cord blood hematopoietic progenitors for unrelated donor hematopoietic progenitor cell transplantation have been included in the total number. These hold a MA license only in the US. Similar products are available in most countries as cell transplants and not as marketed products. The number of products presented in this figure does not include either products with RMAT designation (USFDA) or products with suspended MA. GVHD, graft-versus-host disease.

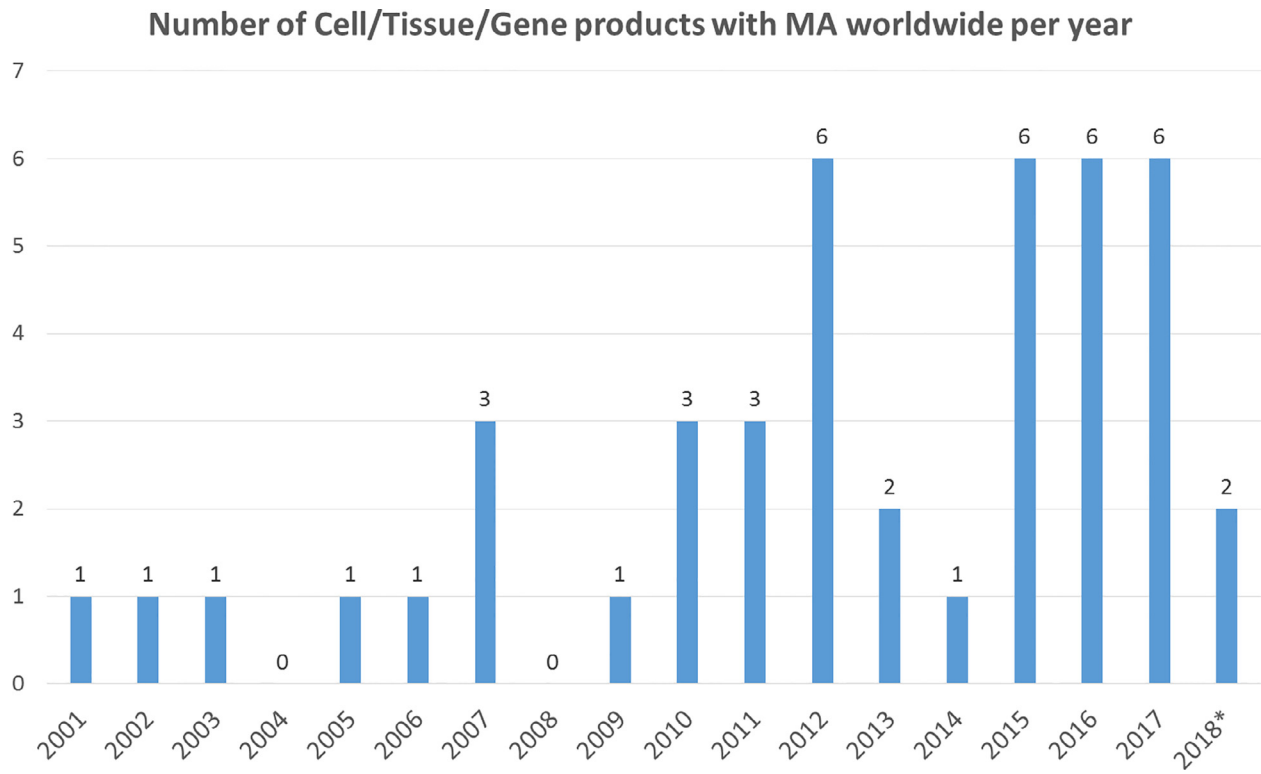

Figure 3. Cell, tissue and gene products with MA worldwide (44 unique products) organized by year of MA. Eight products based on cord blood hematopoietic progenitors for unrelated donor hematopoietic progenitor cell transplantation have been included in the total number. These hold a MA license only in the US. Similar products are available in most countries as cell transplants and not as marketed products. The number of products presented in this figure does not include either products with RMAT designation (USFDA) or products with suspended MA.

completing the project. We are grateful to Doug Sipp (RIKEN, Kobe, Japan) for his help with MA status of cell, gene and tissue products in East Asia.

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