



# REGULATION OF ADVANCED THERAPY MEDICINAL PRODUCTS: CONCEPT NOTE AND RECOMMENDATIONS

Ninth Conference of the Pan  
American Network for Drug  
Regulatory Harmonization (PANDRH)



San Salvador,  
24 to 26 October, 2018

# PAHO

**PANDRH** Pan American Network for Drug Regulatory Harmonization





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**Washington, D.C., 2019**

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# CONTENTS

Acknowledgments	<b>5</b>
Acronyms	<b>6</b>
Glossary	<b>7</b>
Summary	<b>8</b>
Background	<b>8</b>
Main regulatory challenges	<b>9</b>
Classification of advanced therapy products	<b>10</b>
Progress in the regulation of advanced therapy medicinal products	<b>11</b>
a. Factors to consider in a risk-based approach to advanced therapy products	<b>11</b>
b. Significant risks to be addressed as part of regulation	<b>11</b>
c. General considerations: Establishment of the basis for regulation of advanced therapy medicinal products	<b>12</b>
d. General considerations: Approval of advanced therapy medicinal products	<b>13</b>
e. General considerations: Post authorization of advanced therapy medicinal products	<b>13</b>
Recommendations for Regulatory Authorities	<b>14</b>
References	<b>16</b>

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## ACRONYMS

<b>ALIFAR</b>	Latin American Association of Pharmaceutical Industries
<b>ANVISA</b>	National Agency for Health Surveillance (Brazil)
<b>ARCSA</b>	National Agency for Regulation, Control and Health Surveillance (Ecuador)
<b>CPANDRH</b>	Conference of the Pan American Network for the Harmonization of Pharmaceutical Regulation
<b>FDA</b>	Food and Drug Administration (United States)
<b>GCP</b>	Good clinical practices
<b>GLP</b>	Good laboratory practices
<b>GMP</b>	Good manufacturing practices
<b>HIV / AIDS</b>	Human immunodeficiency virus/acquired immunodeficiency syndrome
<b>INVIMA</b>	National Institute for Food and Drug Surveillance (Colombia)
<b>NRA</b>	National Regulatory Authority
<b>PAHO</b>	Pan American Health Organization
<b>PANDRH</b>	Pan American Network for the Harmonization of Pharmaceutical Regulation
<b>WHO</b>	World Health Organization

## GLOSSARY

**Biopharmacovigilance:** This process is intended to detect, notify and record incidents and adverse reactions that may arise from the therapeutic use of human tissues to obtain maximum information and apply appropriate corrective measures to minimize risks.

**Medical products of human origin:** they cover all biological materials derived totally or partially from the human body that are destined for a clinical application. These are anatomical components, as well as secretions or excretions from living or deceased people.

**Xenogenic donor:** Transplant performed with organs or tissues from a donor of a different species than the recipient.



## SUMMARY

The aim of this document is to highlight the progress made with regard to advanced therapy products, the risks associated with such products, and the regulatory challenges they pose for Member States with a view to strengthening regulatory systems. The document is also a call to action for governments to consider the development of standards and rules for regulating these products in order to control the use of unapproved therapies and prevent risks to the population. As discussed, there are cross-cutting regulatory principles that should be implemented by any regulatory body that plans to undertake the regulation and oversight of advanced therapy products.

## BACKGROUND

Since the 1980s, blood stem cells have been used to treat diseases and conditions of the blood and immune system or to restore the blood system after treatments for specific cancers. Skin stem cells have been used to develop skin grafts for patients with severe burns over extensive areas of the body. These stem-cell-based therapies have been deemed safe and effective treatments and are considered conventional therapies (1).

However, recent scientific knowledge concerning the possibility of manipulating cells has opened a very promising field for science and regenerative medicine and has led to the development of new products of human origin that could be used as advanced therapies. However, it is important to note that most of these therapies are still in the experimental phase and few have been approved for clinical use, owing, among other reasons, to insufficient evidence of their safety and efficacy (2). Notwithstanding, in the Region of the Americas there has been a proliferation of for-profit centers that promise people access to cell-based therapies. In many cases, these centers are oriented towards medical tourism.

These centers promote treatments and therapies that have not been approved by regulatory agencies that have the capacity to evaluate the safety, efficacy, and quality of the advanced therapy products offered. Many of these centers are being set up in places with little or no regulation and/or oversight on the part of the health authorities involved in monitoring such medical practices and/or the national authorities responsible for regulating drugs and other health technologies and products for therapeutic use. Because they are using methods and products without any solid scientific basis, these centers are not contributing any value to the health system. Moreover, treatments with these products entail clinical risks for the patients who receive them and reputational risks to the health authorities who grant licenses to these centers (3).

In 2018, the Pan American Health Organization/World Health Organization (PAHO/WHO) received a series of queries and requests for technical cooperation relating to the issuance of recommendations on the regulation of advanced therapy medicinal products and the authorization of establishments that offer treatments using such products. In response, PAHO/WHO prepared a concept note on the topic entitled “Current Status

of the Regulation of Advanced Therapy Medicinal Products,” which put forward recommendations that were discussed and adopted at the Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (CPANDRH), held in San Salvador, El Salvador, in October 2018 (4).

The paragraphs below summarize the additional information contributed by PANDRH members with a view to making public the recommendations adopted by Network members. They highlight the progress made with regard to advanced therapy products, the risks associated with them, and the regulatory challenges they pose to Member States. This information is provided to promote the strengthening of regulatory systems and conveying the recommendations on the subject adopted at the Ninth CPANDRH.

## MAIN REGULATORY CHALLENGES

The ongoing advance of scientific research generally keeps it several steps ahead of regulatory mechanisms. The distance between research and the possible application or use of the research findings has been considerably reduced through easier access to information and knowledge. However, this poses significant challenges for governments, health services, and physicians desiring to utilize these new products with the confidence that they are safe and efficacious. Patients also wish to have timely access to these types of therapies, which promise to treat or control health conditions for which no treatment is currently available (1, 2, 5). Some of the main challenges that regulatory authorities today face are:

- 1)** The need to develop adequate mechanisms to regulate these new products, considering the scientific advances, benefits, and risks associated with them. It must be recognized that these treatments entail clinical risks for the patients who receive them. Despite the enormous amount of research being conducted, there are still few safe and efficacious treatments available to patients. As with any innovative technology, all treatments should be considered experimental until all stages of the clinical trials needed to demonstrate their safety and clinical benefit have been completed. Only then can a treatment be approved for widespread use (5, 6).
- 2)** Treatments with advanced therapy products are all specialized procedures. They should be carried out only in specialized centers authorized by national health authorities. There are different regulatory perspectives on the development and use of these therapies in terms of safety, health needs, idiosyncrasy, and technology, among other considerations (5, 7). Some institutions are advertising “stem-cell products” that have not been rigorously approved by national regulatory agencies and are not based on solid scientific evidence.
- 3)** Government regulatory systems are still developing and do not provide clear and specific regulations for the use, management, monitoring, and follow-up of these therapies. The ethical implications for donors, patients, and governments must be considered, as well as the reputational risk to governments

that license products or therapies that lack demonstrated benefits, efficacy, and safety, and to the centers that administer such products (8).

## CLASSIFICATION OF ADVANCED THERAPY PRODUCTS

WHO has defined medical products of human origin as all biological materials that are derived wholly or in part from the human body and are intended for clinical application (6). Some regulatory agencies have adopted this classification, considering advanced therapy medicinal products to be medicines for human use, obtained from cells (cell therapy), genes (gene therapy), or tissue (tissue engineering), including products of autologous, allogenic, and even xenogeneic origin (5, 9, 10).

Somatic cell therapy products contain (asexual) cells or tissues that have been manipulated to change their biological characteristics or cells or tissues that are not intended to be used for the same essential functions they performed in the donor. They can be used to cure, diagnose, or prevent diseases. An example of somatic cell therapy is the use of a patient's manipulated cancer cells to fight remaining cancer cells in the body (10).

Gene therapy products contain genes that have a therapeutic effect. They insert "recombinant" genes into cells, frequently using a virus as a vector (vehicle used to transfer genetic material to a target cell). When the gene enters the patient's cells, the cells produce a protein that may help to slow down or cure a disease, such as a genetic disorder or cancer (10).

Tissue-engineered products consisting of human cells organized in tissues or organs that have properties that allow regenerating, reconstituting or replacing a human tissue or organ, in the presence or not of structural support consisting of biological or biocompatible material, and has been subjected to substantial manipulation; and/or performs in the recipient a function distinct from that performed in the donor. An example of a tissue-engineered product is artificial skin used to treat patients with burns (10-12).

Finally, there are combined advanced therapy medicines, which contain one or more medical devices as an integral part of the medicine or one or more active implantable medical devices. Their cellular or tissue part must contain (viable or non-viable) cells or tissues whose action in the human body can be considered primary to these devices.

## PROGRESS IN THE REGULATION OF ADVANCED THERAPY MEDICINAL PRODUCTS

As has been pointed out in various publications and in a 2018 editorial in the journal Nature, the properties and functions of cells can be harnessed to identify and treat disease. Nevertheless, as the editorial notes, despite the promises of cell therapies, very few cell products have been approved for clinical use. One of the main reasons is that cell therapies have failed to provide sufficient safety and efficacy guarantees (2). It is therefore essential to establish appropriate regulatory frameworks and pre-and post-authorization oversight activities for cell- and tissue-derived therapy products in order to prevent unauthorized uses of these types of therapies.

To date, the drug regulatory agencies of the following countries have classified these products as medicines and have therefore established or are developing a specific framework for their regulation: Canada, United States, Korea, Singapore, Japan and European Union (9).

Given the challenges that the regulation of this type of products poses, such regulations are formulated through an approach based on the risk that they represent for public health. Presented below are general and specific considerations/recommendations that could be considered both for the establishment of regulatory frameworks and in the process of approving this type of product or in the post-marketing surveillance stage. These considerations are based on a review of regulatory progress in this area; there may be others that are not included in this document (9).

### **a. Factors to consider in a risk-based approach to advanced therapy products:**

In a risk-based approach to addressing advanced therapy products with therapeutic goals, the following aspects should be considered: 1) Prevent and control inappropriate manipulation or processing that can damage or contaminate autologous or heterologous tissues or cells; 2) Ensure the clinical safety of all tissues and cells that are processed, used for functions other than their normal functions, combined with non-tissue components, or used for metabolic purposes; and 3) Prevent the use of contaminated tissues or cells (for example, contaminated with HIV/AIDS or hepatitis).

### **b. Significant risks to be addressed as part of regulation:**

There are four significant risks to be addressed as part of regulation of advanced therapy products: 1) Risk of infection due to microorganism contamination or reactivation; 2) Risk of accidental exposure of health professionals and caregivers to the treatment; 3) Violation of the rights of live donors due to lack of information; and 4) Administration to patients of advanced therapy products whose safety and/or efficacy has not been verified.

As the extent of cell manipulation poses the greatest risk in terms of public health, is important to highlight the difference between the concepts of minimal manipulation and substantial manipulation of cells:

**Minimal manipulation** means that cells or tissues are processed using a technique that does not significantly alter their biological characteristics, including differentiation and activation state, proliferation potential, and metabolic activity (10, 11).

Minimal manipulation techniques include cutting, separating, centrifuging, soaking or preserving in antibiotic solutions, concentrating, purifying, filtering, lyophilizing, irradiating, freezing, cryopreserving and vitrifying, among others that meet the above definition. Stem cell processing for purposes of conventional transplantation is considered minimal manipulation of cells.

**Substantial manipulation** means that cells and tissues are processed in a way that alters any of their biological characteristics, including differentiation and activation state, proliferation potential, and metabolic activity. In this context, any type of cell culture is considered substantial manipulation (10, 11).

The risk is considered smaller if the cells are of autologous origin (from the individual him/herself) rather than of allogenic origin (obtained from a donor).

For advanced therapy medicines, a high risk is generally considered to exist when a) the product has been extensively or substantially manipulated; b) the product is intended for non-homologous use—i.e., it is to be used for a function different from its original function; or c) the product is combined with or used together with a drug, biological, or device.

### **c. General considerations: Establishment of the basis for regulation of advanced therapy medicinal products**

In general, the various recommendations for the regulation of this type of medicines consider the following aspects to be important: a) cells subjected to substantial manipulation in the laboratory or that perform a function in the recipient that is different from the function performed in the donor pose a high intrinsic risk to the health of those who use them, and related clinical research on and therapeutic use of such cells requires a regulatory framework that includes the prior approval of regulatory agencies; b) the origin of the cells (autologous or allogenic) has less impact on risk assessment than the degree of manipulation to which the cells have been subjected. The risk of transmission of infectious agents in allogenic products should be considered; c) there is a significant difference between the regulatory framework for cells subjected to minimal manipulation that are intended to perform the same function in the recipient as in the donor, and the regulatory framework for cells subjected to minimal manipulation but intended to perform a function in the recipient that is different from that performed in the donor (12-14).

Some regulatory authorities exempt products of autologous origin from the application of health standards applied to other advanced therapy products if they are processed according to quality and safety requirements, under medical responsibility, in the hospital context.

This regulation also requires the ministry of health or the competent health authority to regulate the clinical

use of such therapies and the institutions that propose to use them. The regulation of these therapies may require linkage or coordination between different entities or organizations of a country's health system.

#### **d. General considerations: Approval of advanced therapy medicinal products**

In general, advanced therapy medicinal products classified as high-risk must meet the same premarket approval requirements as those applied by national regulatory authorities to other medicines. Accordingly, the following requirements are considered important for the authorization of such products (13-15): a) information on quality (data on the inputs and raw materials used to produce the product, quality validation and control, stability, and maintenance of traceability, etc.); b) adherence to good manufacturing practice (GMP), good laboratory practice (GLP), and good clinical practice (GCP); and c) development of clinical trials to determine whether a proposed treatment is safe and effective and offers improvements over existing treatments.<sup>1</sup>

For advanced therapy medicinal products deemed to be low risk, because they are subject to minimal manipulation but intended to perform a function in the recipient that is different from that performed in the donor, the following requirements are considered: a) authorization of the facility to process these products; b) evidence of informed consent from the patient prior to the administration of the products; c) adequate documentation and registration of all products, including information on their intended purposes and information on donation, acquisition, and testing carried out on these products.; d) existence of an identification system that allows product traceability from donor to recipient and vice versa; and e) adherence to good manufacturing practice (GMP) and good laboratory practice (GLP) and good clinical practice (GCP) (12, 15, 16).

Clinical trials should be notified to the defined regulatory authority and approval will be made in accordance with evidence of clinical safety and efficacy, and certification of the requirements described.

#### **e. General considerations: Post authorization of advanced therapy medicinal products**

After authorization, the product may be used in a large number of patients over an extended period, sometimes in conjunction with other medicines. Certain side effects may arise in such circumstances. At the time of authorization of a medicine, the evidence of its safety and efficacy is limited to the results of clinical trials, in which patients are carefully selected and closely followed under controlled conditions. This means that the product has been tested in a relatively small number of selected patients for a limited time.

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<sup>1</sup> Several clinical trials involving pluripotent stem cells are underway or have been completed. The principal areas in which progress has been made are: macular degeneration; neurological conditions such as Parkinson's disease, Huntington disease, and motor neuron disease; diabetes; spinal cord injury (endparalysis.org has a good summary of clinical trials, and the European Spinal Cord Injury Federation has useful advice on unproven therapies); myocardial infarction (closerlookatstemcells.org has updated information on stem cells and the heart); diseases or areas with new clinical trials or trials in progress or completed involving tissue stem cells; multiple sclerosis therapy using blood stem cells; leukemia studies; and cartilage or tendon injuries. There are numerous other clinical trials to test specific medicines designed to stimulate stem cell growth in the body of the patient in order to derive cells or cell lines to be used in research and clinical trials.

Consequently, it is essential that the safety of all authorized medicines be continually monitored while they are used in medical practice. The regulatory authority should consider developing a pharmacovigilance system for these medicines in which all product authorization holders should participate. To that end, the product authorization holder should have a system for compiling, processing, and evaluating information on suspected adverse reactions and communicating this information to the regulatory authority. This will enable the early detection of risks and the effective mitigation of their consequences for patients and will contribute to the design of appropriate post-authorization studies to monitor the safety and efficacy of products (12, 13, 16).

Finally, it is important to highlight the need to develop regulations for this type of therapies, bearing in mind that continual advances in scientific research generally keep it several steps ahead of regulatory mechanisms, a situation that occurs worldwide. Accordingly, ongoing communication and coordination between scientific and regulatory entities is needed to achieve the harmonization of standards, guidelines, regulations, and mechanisms for simultaneous adoption in different countries. The dissemination of information and knowledge concerning approved uses, possible risks, and the possibilities for generating transformative and potentially curative treatments using advanced therapies will facilitate the control of such therapies.

## RECOMMENDATIONS FOR REGULATORY AUTHORITIES

The Ninth Conference of the Pan American Network for Drug Regulatory Harmonization recommends to the regulatory authorities

- 1.** Strengthen the regulatory systems for medicines, health technologies, and products of human origin through:
  - a.** Review of national regulatory frameworks by NRAs, and recognition of the existence of such products;
  - b.** Adoption of specific regulations for the introduction of advanced therapies, considering the Guiding Principles on human cell, tissue and transplantation and the Principles on the donation and management of blood, blood components and other medical products of human origin, both established by WHO and other international guidelines;
  - c.** Use of international standards for approval of these therapies, registration of products, and licensing of establishments that manipulate or administer them (including but not limited to: clinical trials of effectiveness, safety, and efficacy; monitoring of good manufacturing practices; bio pharmacovigilance, etc.);

**d.** Authorization (including licensing or when appropriate), supervision and surveillance of the centers or facilities in those cases where it is demonstrated that approved cell therapy techniques are used, in order to avoid fraudulent activities.

**2.** Improve information mechanisms in regulatory authorities in order to:

**a.** Inform the community about the uses, risks, and benefits of therapies based on the current scientific evidence in order to prevent misleading advertising;

**b.** Urge physicians and patients not to use unapproved stem cells for therapeutic purposes, given the possible risks of such therapy;

**c.** Expand the network for communication between regulatory agencies, investigators, centers, and other interested parties in order to maintain continuous communication and coordination to achieve the harmonization of standards, guidelines, regulations, and implementation mechanisms, and improve the production of data on the regulation and use of these products and the exchange of information on safety.



## REFERENCES

1. Mahla RS. Stem cells application in regenerative medicine and disease therapeutics. *Int J Cell Biol*. [Internet]. 2016 [accessed 17 July 2019]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/>
2. Towards advanced cell therapies [editorial]. *Nature Biomedical Engineering* 2018;2:339–340. Available from: <https://doi.org/10.1038/s41551-018-0256-4>
3. FDA Statement. Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA's new policy steps and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine. [Internet] 2017. [accessed 17 June 2019]. Available from: <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-new-policy-steps-and-enforcement-efforts-ensure>
4. Pan American Health Organization, Department of Health Systems and Services, Medicines and Health Technologies Unit. Desafíos de la regulación de productos de terapia celular: situación Regional y recomendaciones [Presentation given at the IX Conferencia de la Red Panamericana para la Armonización de la Reglamentación Farmacéutica (CPARF)]. San Salvador: PAHO; 2018. Available from: [https://www.paho.org/hq/index.php?option=com\\_docman&view=download&category\\_slug=ix-cpandrh&alias=46996-desafios-de-la-regulacion-de-productos-de-terapia-celular-situacion-regional-y-recomendaciones-mauricio-beltran-duran-asesor-regional-servicios-de-sangre-y-trasplantes-unidad-de-medicamentos-y-tecnologias-sanitarias-sistemas-y-servicios-de-salud-mt&Itemid=270&lang=en](https://www.paho.org/hq/index.php?option=com_docman&view=download&category_slug=ix-cpandrh&alias=46996-desafios-de-la-regulacion-de-productos-de-terapia-celular-situacion-regional-y-recomendaciones-mauricio-beltran-duran-asesor-regional-servicios-de-sangre-y-trasplantes-unidad-de-medicamentos-y-tecnologias-sanitarias-sistemas-y-servicios-de-salud-mt&Itemid=270&lang=en)
5. International Pharmaceutical Regulators Forum, Cell Therapy Working Group. Cell therapy [Internet]: IPRF; 2019 [accessed 12 September 2019]. Available from: <http://www.iprp.global/working-group/cell-therapy>
6. World Health Organization. Principles on donation and management of blood, blood components and other medical products of human origin [Internet]. 70th World Health Assembly; 2017; Geneva. Geneva: WHO; 2017 (agenda item 13.2. Document A70 / 19) [accessed 16 July 2019]. Available from: [https://apps.who.int/iris/bitstream/handle/10665/274793/A70\\_19-en.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/274793/A70_19-en.pdf?sequence=1&isAllowed=y)
7. Red/Consejo Iberoamericano de Donación y Trasplante. Declaración de Quito sobre terapias celulares sin evidencia demostrada. *Trasplante Iberoamérica* 2017;11(1):13–23. Available from: [https://issuu.com/on-t/docs/newsletterrcidt2012\\_pdf](https://issuu.com/on-t/docs/newsletterrcidt2012_pdf)

- 8.** Ochoa M, Merck B, Villar V, García D, Ciangherotti C. Estado de la cuestión, aspectos conceptuales y de regulación sobre el uso de la terapia celular en la Unión Europea y en los Estados miembros de la Red/ Consejo Iberoamericano de Donación y Trasplante. Newsletter Trasplante Iberoamérica. 2017;XI(1): 13-24. Available from: [http://www.ont.es/publicaciones/Documents/NEWSLETTER%20IBEROAMERICA-2017\\_baja.pdf](http://www.ont.es/publicaciones/Documents/NEWSLETTER%20IBEROAMERICA-2017_baja.pdf)
- 9.** Srinivasan N. Kellathur, Huei-Xin Lou, Cell and tissue therapy regulation: Worldwide status and harmonization, *Biologicals*, 2012;40(3):222-224. [accessed 18 July 2019]. Available from: <http://www.sciencedirect.com/science/article/pii/S1045105612000243>
- 10.** European Medicines Agency. Committee for Advanced Therapies (CAT). Available from: [https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products\\_en-O.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-O.pdf)
- 11.** Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Available from: [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg\\_2007\\_1394/reg\\_2007\\_1394\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf)
- 12.** Parca RM et al. Marco regulatório produtos terapias avançadas. *Vigil. sanit. debate* 2018;6(1):15-22. Available from: <http://portal.anvisa.gov.br/documents/4048533/5234972/Revista+Visa+em+debate+-+Marco+regulat%C3%B3rio+para+Produtos+de+Terapia+Avan%C3%A7ada+no+Brasil+2018/5299e703-c191-4a5c-88cd-33c323f1d9a3>
- 13.** Singapore's Ministry of Health, Health Sciences Authority. Guidance on therapeutic product registration in Singapore [Internet]: HSA ; 2019 [assessed 12 September 2019]. Available from: [https://www.hsa.gov.sg/content/hsa/en/Health\\_Products\\_Regulation/Western\\_Medicines/Overview/Guidelines\\_on\\_Drug\\_Registration.html](https://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Western_Medicines/Overview/Guidelines_on_Drug_Registration.html)
- 14.** Japan Pharmaceutical Manufacturers Association, Regulatory Information Task Force. Pharmaceutical Administration and Regulations in Japan: Information on Japanese Regulatory Affairs. Japan: JPMA; 2019. Available from: <http://www.jpma.or.jp/english/parj/pdf/2019.pdf>
- 15.** United States Food and Drug Administration. Minimal Manipulation and Homologous Use Guidance for Industry and Food and Drug Administration Staff. Silver Spring, MD; Food and Drug Administration; 2017. Available from: <https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585403.pdf>
- 16.** España, Ministerio de Sanidad, Servicios Sociales e Igualdad. Real Decreto 477/2014, de 13 de junio, por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial. In: *Boletín Oficial del Estado* 2014; 144: 45068-45078. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2014. Available from: [https://www.boe.es/diario\\_boe/txt.php?id=BOE-A-2014-6277](https://www.boe.es/diario_boe/txt.php?id=BOE-A-2014-6277)

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