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Study on the regulation of advanced therapies in selected jurisdictions

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List of abbreviations

ACA	Affordable Care Act
AMED	Agency for Medical Research and Development
ANDA	Abbreviated New Drug Application
ASP	Average Selling Price
ATMP	Advanced therapy medicinal product
BGTD	Biologics and Genetic Therapies Directorate
BHB	Biopharmaceutical and Herbal Medicine Bureau
BHED	Biopharmaceuticals and Herbal Medicine Evaluation Department
BLA	Biologics License Application
CADTH	Canadian Agency for Drugs and Technologies in Health
CAT	Committee on Advanced Therapies
CBE	Centre for Biologics Evaluation
CBER	Centre for Biologics Evaluation and Research
CCRM	Centre for Commercialization of Regenerative Medicine
CDER	Centre for Drug Evaluation and Research
CDR	Common Drug Review
CDRH	Centre for Devices and Radiological Health
CECR	Centres of Excellence for Commercialization and Research
CERB	Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics
CFR	Code of Federal Regulations
CIPO	Canadian Intellectual Property Office
CIRM	California Institute for Regenerative Medicine
CMC	Chemistry, manufacturing, and control
CMS	Centres for Medicare and Medicaid Services
CPAC	Central Pharmaceutical Affairs Advisory Committee
CSIMC	Central Social Insurance Medical Council
CTA	Clinical Trial Applications
CTD	Common Technical Document
CTN	Clinical Trial Notification
CTOR	Safety of Human Cells, Tissues and Organs for Transplantation Regulations
DBCAC	Drug Benefit Coverage Assessment Committee
DIN	Drug Identification Number
DNA	Deoxyribonucleic acid
DOD	Department of Defence
DRG	Diagnosis-Related Group
EC	European Commission
EMA	European Medicines Agency
ERB	Ethical Review Board
ERP	External Reference Pricing
EU	European Union
EXCITE	Excellence in Clinical Innovation Technology Evaluation
FD&C	Federal Food, Drug, and Cosmetic Act
FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDCA	Food, Drug & Cosmetics Act
FDR	Food and Drug Regulations
FIRM	Forum for Innovative Regenerative Medicine
FIRST	Funding Program for World-Leading Innovative R&D on Science and Technology
GAO	Government Accountability Office
GCP	Good Clinical Practice

GCT	Gene, cell and tissue
GCTP	Good, gene, Cellular and Tissue-based product manufacturing Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSRAC	Global Stem Cell and Regenerative Medicine Acceleration Centre
GTP	Good Tissue Practice
GVP	Good Vigilance Practice
HCT/Ps	Human cell, tissue and cellular and tissue-based product
HDAP	Human Drug Advisory Panel
HDE	Humanitarian Device Exemption
hES	human Embryonic Stem cell
HIRA	Health Insurance Review and Assessment service
HPB	Health Policy Bureau
HSC	Health Science Council
HTA	Health Technology Assessment
HTSCA	Human Tissue Safety and Control Act
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IIT	Investigator Initiated Trial
IND	Investigational New Drug
IPR	Intellectual property rights
iPS	induced Pluripotent Stem cells
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITA	Investigational Testing Authorisation
J-GCP	Japanese Good Clinical Practice
JPO	Japan Patent Office
J-RMP	Japanese Risk Management Plan
JSPS	Japanese Society for the Promotion of Science
JST	Japan Science and Technology Agency
KFDA	Korea Food and Drug Administration
KIPO	Korea Intellectual Property Office
KIPRIS	Korean Intellectual Property Rights Information Service
KNHI	Korean National Health Insurance
KNIH	Korea National Institute of Health
KPO	Korean Intellectual Property Office
MDA	Medical Device Act
MDB	Medical Devices Bureau
MDED	Medical Device Evaluation Department
MDR	Medical Devices Regulations
MDSB	Medical Device Safety Bureau
METI	Ministry of Economy, Trade and Industry
MEXT	Ministry of Education, Culture, Sports, Science and Technology
MFDS	Ministry of Food and Drug Safety
MHLW	Ministry of Health, Labour and Welfare
NCD	National Coverage Determination
NCE	New Chemical Entity (drug)
NCoE	Networks of Centres of Excellence
NCSR	National Centre for Stem Cell and Regenerative Medicine
NDA	New Drug Application
NDS	New Drug Submission
NECA	National Evidence-based healthcare Collaborating Agency
NEDO	New Energy and Industrial Technology Development
NHI	National Health Insurance

NIBIO	National Institute of Biomedical Innovation
NIFDS	National Institute of Food and Drug Safety
NIH	National Institute of Health
NOC	Notice of Compliance
NOC/c	Notice of Compliance with conditions
NOD	Notice of Deficiency
OCP	Office of Combination Products
OCTGT	Office for Cellular, Tissue and Gene Therapies
OCTP	Office of Cellular and Tissue-based Products
ODA	Orphan Drug Act
OPML	Office of Patented Medicines & Liaison
PAA	Pharmaceutical Affairs Act
PBM	Pharmacy Benefit Managers
pCODR	pan-Canadian Oncology Drug Review
PDP	Prescription Drug Plan
PDUFA	Prescription Drug User Fee Act
PFSB	Pharmaceutical and Food Safety Bureau
PHSA	Public health Services Act
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMA	Premarket Approval
PMC	Post-marketing Commitments
PMD Act	Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act
PMDA	Pharmaceuticals and Medical Device Agency
PMPRB	Patented Medicines Pricing Review Bureau
PMR	Post-Marketing Requirements
PSUR	Periodic Safety Update Report
R&D	Research & Development
RFD	Request for Designation
RM Act	Act on the Safety of Regenerative Medicine
RMIT	Regenerative Medicine Industrialization Task Force
RMP	Risk management Plan
RP-PRV	Rare Paediatric Disease Priority Review Voucher
RRABP	Regulation on Review and Authorisation of Biological Products
CN	Stem Cell Network
SEED	Scientific Excellence through Exploration and Development
SME	Small and Medium-sized Enterprise
TPD	Therapeutics Products Directorate
TSE	Transmissible Spongiform Encephalopathies
UCPA	Unfair Competition and Trade Secret Protection Act
UK	United Kingdom
US	United States
USPTO	United States Patent and Trademark Office
VA	Department of Veteran Affairs

Executive summary

This study concerns advanced therapies, which can be briefly defined as innovative medical products for human use based on genes, cells and tissues. The scope of the study includes the current regulatory framework in force for advanced therapies in four selected jurisdictions: United States (US), Canada, Japan, and South Korea. The analysis includes new provisions that have been adopted but have not yet entered into force. Key aspects in the study were predetermined and include the scope of advanced therapy regulation, regulation for clinical trials, marketing authorisation, manufacturing and quality requirements, post-marketing requirements, and regulatory pathways to gain access to advanced therapy treatment outside of clinical trials and to marketed products. In addition, the study includes an overview of research activities and availability of advanced therapies and an analysis of economic aspects of the advanced therapies market in the four jurisdictions. The economic aspects discussed include relevant intellectual property rights (IPR) legislation; incentives to support developers of advanced therapies; the average approval procedure time and time to be commercialised after approval of selected products; and a quick scan on pricing and reimbursement policies that exist in each of the jurisdictions.

Data were collected through desk research of regulatory and other relevant documents by an extensive literature search in peer-reviewed (e.g. PubMed, Web of Science) and clinical trial databases (**data lock point: 31 December 2014**), and from interviews with relevant regulatory bodies and other key stakeholders in each jurisdiction. After the initial data collection period, follow up surveys were sent out to all relevant stakeholder groups in order to verify findings and to collect additional information.

Analysis of the regulatory frameworks governing advanced therapies

The analysis revealed a high degree of convergence in the regulation of advanced therapies in the four jurisdictions. In **Canada, US** and **South Korea** most advanced therapies are regulated within the framework of the medicinal products legislation (category of biologic products). This means that prior individual authorisation is required before they can be marketed. Typically, in marketing authorisation procedures consideration is given to the specific characteristics of advanced therapies, often in close consultation with developers. Traditionally, **Japan** also regulated advanced therapies as medicines but, since 2014, a specific framework for advanced therapies was enacted. It consists of a distinct framework established for academic research that co-exists with a distinct marketing authorisation pathway for advanced therapies in a separate section of the medicines framework.

The definition of “advanced therapy” used for the purpose of this study corresponds to the EU definition of advanced therapy medicinal product. While, for the most part, this concept corresponds also to gene- cell-, and tissue-based products that are regulated as medicines in the four jurisdictions analysed, there are some differences when it comes to certain subtypes of cell-, and tissue-based therapies:

- In **Canada and US** all advanced therapies are regulated as medicines (biologic products). However, the definitions used in Canada and US are broader than the definition of advanced therapies used in this report, meaning that some other types of cell-, and tissue-based products also require marketing authorisation (e.g. minimally manipulated therapies for homologous use that have systemic effects and depend on their metabolic action for primary functions);
- In **South Korea** advanced therapies are regulated as medicines (biologic products), with the exception of minimally manipulated therapies processed in medical centres for non-homologous use. However, certain cell-, and tissue-based products that are

not covered by the definition of advanced therapies used in this study (e.g. minimally manipulated therapies processed by industry for homologous use) are regulated as medicines (biologic products) in South Korea;

- In **Japan**, advanced therapies are regulated as regenerative medicine products in a separate section of the framework for various medicinal products. The concept of advanced therapy corresponds to the concept of regenerative medicine products.

Regulations for biologic products are comparable across Canada, US and South Korea To obtain marketing authorisation it is required to provide confirmatory quality, safety and efficacy data to demonstrate a positive risk/benefit profile. Furthermore, developers have to adhere to process standards such as Good Clinical Practice and Good Manufacturing Practice (GMP), which often contain jurisdiction specific elements. Specific risks that originate from using viable human or animal source material, such as the spread of infectious diseases, are controlled by additional manufacturing and quality regulations such as those that mandate donor screening, donor testing and record keeping and that ensure traceability. The regulations for using viable human or animal source material are generally not harmonized across jurisdictions.

In addition to the regulatory context, all three jurisdictions provide guidance to developers of advanced therapies. Guidelines differ across jurisdictions but generally specify manufacturing and quality standards for advanced therapies and considerations for preclinical and clinical study design. In each of the three jurisdictions, regulatory authorities ultimately determine the type of studies and evidence that is required for marketing authorisation on a case-by-case basis with due consideration of product specific characteristics. Once advanced therapies are authorised, they need to adhere to post-marketing requirements that are similar to other authorised biologic products.

In **Japan**, advanced therapies that are developed for the purposes of marketing are regulated under the medicines framework (Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act, or PMD Act), which is also comparable to the frameworks that exist in Canada, US and South Korea. However, this framework has a new time limited conditional approval pathway specifically for advanced therapies. Japan also enforces specific manufacturing and quality requirements for advanced therapies, which are known as Good, gene, Cellular and Tissue-based product manufacturing Practice (GCTP). This framework co-exists with a distinct framework for clinical research for academic purposes (the Act on the Safety of Regenerative Medicine, or RM Act). Data collected under the RM Act cannot be used for marketing authorisations because process standards – including GCP - are lower compared to the PMD Act.

Access to advanced therapies outside clinical trials and treatment with marketed products is limited to compassionate use programmes in **Canada, US and South Korea**. In contrast, patients can be treated under the RM Act in **Japan**. Similar to other jurisdictions, a general compassionate use programme under the PMD Act can also be used for advanced therapies.

Overview of research activities and availability of advanced therapies

In the **US** we found 132 ongoing research projects on advanced therapies (10,6% phase II-III or III trials) and 5 available advanced therapies. In October 2015, one more product was approved by the U.S. Food and Drug Administration. In **Canada** 39 research projects were ongoing (15,4% phase II-III or III trials) and one advanced therapy is approved. In **Japan** 131 research projects on advanced therapies were conducted (2,3% phase II-III or III trials) and two advanced therapies were available.

Since September 2015 there are two more products available in Japan. In **South Korea** 43 ongoing research projects on advanced therapies (14% phase II-III or III trials) were listed and 18 approved advanced therapies. In **most jurisdictions** the majority of the developers involved in research projects are for non-for-profit organisations or academia (US: 74,2%, Japan: 92,4% and South Korea: 74,4%). In **Canada** the involvement of profit and non-for-profit/academic organisations is more balanced (51,3% and 48,7%). With regard to the late phase trials, we found that in the **US and Canada** the majority of all late phase trials are done by for profit organisations (respectively 71,4% and 83,3%). In **Japan and South Korea**, however, we found that for profit organisations appear not to be involved in late phase trials.

Analysis of the economic aspects of the advanced therapies market

In the **US,** substantially manipulated cells are patentable as long as a claim is not encompassing a human being. Whether substantially manipulated cells are patentable in **Canada** is dependent on the origin and the features of the substantially manipulated cell(s). In **Japan** it is only possible to receive a patent when a product is material based (i.e. not for a method). In **South Korea** substantially manipulated cells are patentable according to the statutory requirements that apply to all types of patents. In addition to IPR legislation, several other incentives exist to support developers of advanced therapies. The main mechanisms in **all jurisdictions** include trade secret protection, data exclusivity as well as funds and research networks to stimulate (clinical) research in the field of advanced therapies. Especially, **US, Canada and Japan** stimulate partnerships between researchers and industry through networks. As described above, the jurisdictions have regulatory pathways in place to decrease the time to marketing authorisation.

The period from R&D to a reimbursed advanced therapy can be up to 20 years. The time to approval differs per type of advanced therapy (cell-, tissue or gene based therapy). Also, time to reimbursement differs between the jurisdictions. However, not all advanced therapies that have been granted marketing authorisation are also reimbursed. In the **US**, 3 out of 5 advanced therapies are reimbursed, the approved product in **Canada** is not reimbursed, in **Japan** all approved products are reimbursed and in **South Korea** 4 products are reimbursed, 9 are not reimbursed and the reimbursement status of the other products (5) is not known. The reasons for these divergent practices have not been assessed as part of this study, but may be due to differences in pricing and reimbursement systems, as this is a competency of each jurisdiction. This claim, however, would need to be further investigated.

1. Introduction

This is the Final Report of the 'study on the regulation of advanced therapies in selected jurisdictions' (contract 20147306; RfS Chafea/2014/Health/24). The research was commissioned by the Consumers, Health, Agriculture and Food Executive Agency (Chafea) in the context of the Framework Contract EAHC/2013/Health/01 signed between the consortium, led by Ecorys Nederland BV, and Chafea).

The assignment for Chafea was conducted by Ecorys Nederland BV, and sub-contractor University Utrecht - division of Pharmacoepidemiology & Clinical Pharmacology at the Utrecht Institute for Pharmaceutical Sciences during April 2015 – March 2016.

1.1. Background and context

Pharmaceutical care is a key component of healthcare and the sector itself is an important economic sector in many jurisdictions. Medicinal products save lives and improve the quality of life of people. This also applies to advanced therapy medicinal products (ATMPs).[1] ATMPs are cutting-edge innovations that hold promise for the treatment of a number of diseases with high unmet need, such as skin in burns, Alzheimer's disease, cancer or muscular dystrophy.

The lack of such products puts patients with these diseases at potential and actual risk of suffering undesirable health consequences. Access to health technology can be accelerated by optimising the process of regulatory approval. Pharmaceutical product registration and the interpretation and application of technical guidelines and requirements are harmonised internationally.[2] This is, however, not the case for ATMPs.

1.1.1. Definition of advanced therapy medicinal products

Throughout the report we will use the global term "advanced therapies" to refer to the following therapeutic modalities:

1. Cells or tissues (of human or animal origin) that are administered to human beings with the purpose of:
    a. treating, preventing or diagnosing a disease; or
    b. regenerating, replacing or repairing human cells, tissues or organs with the exception of cells/tissues that have only been subject to minimal manipulation (e.g. cutting, freezing or centrifugation) provided that they are used to maintain the same function in the same anatomical or histological environment in the recipient as in the donor (so-called "homologous use"). For example, non-substantially manipulated bone-marrow cells used for haematopoietic reconstitution in the recipient are not to be considered as advanced therapies. However, if the same cells are used for other purpose (e.g. cardiac repair), they are to be considered as advanced therapies ("nonhomologous use"). Non-viable cells or tissue acting solely through mechanical means will not be considered advanced therapies.
2. Biological products involving the use of recombinant DNA (rDNA) technology to introduce genetic material into a person's DNA to regulate, replace, repair, add or delete faulty or missing genetic material.

1.1.2. Regulation and marketing authorisation of advanced therapies in the EU

The Regulation on advanced therapies (Regulation (EC) No 1394/2007) is the basic legislation for these products. The Regulation was adopted in 2007[3] and effective from 30 December 2008 onwards[4]. The Regulation was accompanied by a series of guidelines issued by the European Medicines Agency (EMA).

In Europe, all advanced therapies are subject to a centralised marketing authorisation procedure. Before marketing authorisation is granted to advanced therapies they are tested extensively in order to prove the quality, safety and efficacy of the products. The Committee on Advanced Therapies (CAT) at EMA conducts the scientific assessment of the quality, efficacy and safety profile and whether the product can be considered an advanced therapy (classifications). Thereafter, an opinion is provided to the EC that decides on the granting of the authorisations at Community level.[5]

Nevertheless, it is possible to treat patients with advanced therapies without official authorisation. Each Member State has the power to make exceptions, provided that it is a therapy adjusted and applied to individual patients and under the responsibility of a medical professional (hospital exemption).

Another essential issue is that the EC has no involvement in the approval of clinical trials. Such approval is the responsibility of the Member States. Because of this allocation of responsibilities, the developers of the therapy are forced to seek contact with authorities at the EC level and the national level. The national authorities are also responsible for the approval of medical devices, which is a separate area. This means, in the case of a therapy using a medical device, an increase in the administrative burden.

To date, six advanced therapies have been granted marketing authorisation in the European Union (EU). Even taking into account the hospital exemption, the actual number of patient treated with advanced therapies and the number of advanced therapies itself are limited. This has led to the perception that the regulatory procedures to develop and authorise advanced therapies is less fit-for-purpose in the EU than in other jurisdictions, such as US, Canada, Japan and South Korea. The European Commission (EC) is interested in these four jurisdictions because US, Canada and Japan have comparable systems in place regarding public health protection. In 2008, the regulatory agencies of Europe (EMA) and US (Food and Drug Administration - FDA) set up a platform to share experiences and discuss regulatory approaches towards advance therapies. Health Canada, the regulatory agency of Canada, joined this so-called ATMP cluster in 2012.[6]

In addition, South Korea is interesting because the country seems to have good systems in place for ATMP regulation.

1.2. Objective

The objective was to produce a study report with comprehensive and factual information about the US, Canada, Japan and South Korea with regard to:

- advanced therapies that are already available to patients;
- those that are in development phase; and
- the regulatory frameworks governing advanced therapies in these four jurisdictions.

The study comprises three main parts (data lock point: 31 December 2014):

- Analysis of the regulatory framework governing advanced therapies in US, Canada, Japan and South Korea;
- Overview of research activities and availability of advanced therapies in US, Canada, Japan and South Korea;
- Analysis of the economic aspects of the advanced therapies market in US, Canada, Japan and South Korea.

1.3. Outline of the report

The report includes our approach and methodology used (Chapter 2). Thereafter, we provide an overview of the regulatory framework governing advanced therapies in the US (Chapter 3), Canada (Chapter 4), Japan (Chapter 5) and South Korea (Chapter 6). In Chapter 7 we present an overview of research activities and the availability of advanced therapies in the selected jurisdictions, while in Chapter 8 we provide the analysis of economic aspects of the advanced therapies market in each jurisdiction. The conclusions are presented in Chapter 9.

The report is supported by the following Annexes:

- Annex 1. Overview of interviews with stakeholders;
- Annex 2. Questionnaire used for exploratory and in-depth interviews;
- Annex 3. Full search strategy and inclusion criteria to provide an overview of research activities and availability of advanced therapies;
- Annex 4. Databases and websites covering authorised clinical trials;
- Annex 5. Full search strategy and inclusion criteria for the analysis of the regulatory framework governing advanced therapies;
- Annex 6. Advanced therapies authorised for commercialisation;
- Annex 7. Clinical trials of advanced therapies in each jurisdiction;
- Annex 8. Full references clinical trials;
- Annex 9. Full search strategy related to the analysis of the economic aspects of the advanced therapies market;
- Annex 10. Status of selected IP legislation in the US (114th Congress).

1.4. References

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2. Approach and methodology

2.1. Exploratory interviews

We conducted exploratory interviews with representatives of the competent authorities presented below.

Table 2.1 Exploratory interviews

Jurisdiction	Competent Authority
Japan	PDMA, Office of Cellular and Tissue based Products
South Korea	Global Stem Cell and Regenerative Medicine Acceleration Centre - GSRAC
Canada	Health Canada, Biologics and Genetic Therapies Directorate

The FDA (Centre for Biologics Evaluation and Research (CBER)) declined to participate in an exploratory interview because many of the topics were felt to be beyond the scope of the Centre or to include information that the Centre is prohibited to disclose. However, the Centre provided information by email. The Ministry of Food and Drug Safety (MFDS) in Japan declined our request for an interview due to lack of manpower. In addition to the exploratory interview, the PMDA provided answers to a follow-up questionnaire and Health Canada reviewed the information provided in Chapter 4.

The exploratory interviews/information directed us towards further relevant source material and key stakeholders in the field for conducting in-depth interviews. Simultaneously, we gained a first impression of the relevant rules governing advanced therapies in each jurisdiction.

In Annex 1 we provide an overview of the (exploratory and in-depth) interviews with relevant stakeholders, while in Annex 2 the questionnaire used is presented.

2.2. Approach to provide an overview of research activities and availability of advanced therapies

The overview of research activities and availability of advanced therapies consists of:

- Advanced therapies that have been authorised for commercialisation in each jurisdiction (presented in Annex 6);
- Authorised clinical trials of advanced therapies in each jurisdiction (presented in Annex 7);
- The developers involved in on-going research projects and/or involved in advanced therapies that are already available including their size and analysis of the relative weight of academia and non-for-profit sector (presented in Annex 6 and 7).

To provide the overview we used several methods, which are described below.

2.2.1. Desk research and literature search

We conducted desk research using relevant official and relevant databases and websites and a literature search to identify relevant publications on research activities and availability of advanced therapies. The data lock point was 31 December 2014. We used a structured search strategy and inclusion criteria for both the desk research and the literature search. The search strategy and exclusion criteria were validated by the client. Relevant articles were identified by means of a search of the bibliographical

databases PubMed, MEDLINE and EMBASE. These databases were searched using MeSH terms, thereafter two reviewers independently scanned the titles and abstracts of the identified publications. Relevant publications were first selected for light reading, after which full texts were obtained. In addition, a search using key words was conducted in Clinicaltrials.gov and country specific databases, the titles and abstracts for the publications were scanned. After removing duplicates, relevant publications were selected for light reading. These full text articles were used to extract relevant information about the clinical trial e.g. clinical trials phase, therapeutic indication, developer, type of organisation.

In Annex 3 we provide our full search strategy and the inclusion criteria used. In Annex 4 we provide the official databases and websites covering authorised clinical trials (and approved advanced therapies). The databases and websites were retrieved through desk research and validated in the interviews.

We conducted desk research on the size of the developers of advanced therapies that are already available to patients or those that are involved in research projects. Information collected include a) number of enterprises by size (number of persons employed), b) type (SME, but also academia, non-for-profit), and c) annual turnover.

2.2.2. Web-based survey and follow-up interviews

In addition, we conducted a (web-based) survey by identifying potential invitees to address the gaps in the evidence available. Each survey invitee received an email containing an invitation letter to participate in the project. The list with relevant information about approved products and clinical trials was presented to relevant stakeholders to validate our findings. We asked respondents to comment on the completeness and correctness of the list, for both advanced therapies and clinical trials. In this survey we also asked about unapproved advanced therapies that are available through other routes (i.e. enrolment in clinical trials, compassionate use programmes, medical practice, etc.).

Efforts were made to ensure a good response rate, with reminder emails sent 14 days after the first invitation to the stakeholders who have not yet responded. A subsequent reminder was sent to all stakeholders who have not responded two weeks after the second reminder.

2.3. Approach to analysis of the regulatory frameworks governing advanced therapies

We used a two-step approach consisting of (1) desk research and (2) in-depth interviews. All covered issues are summarised in Table 2.2, including references to the sections in Chapter 3-6 in which they are further outlined.

Table2.2 Aspects covered on the basis of desk research and interviews

Aspects covered on the basis of desk research and interviews
1. Examination of routes for patients to have access to advanced therapies (Chapter 3-6, Section 6): a. Description of existing routes for patients to have access to advanced therapies that have not been approved for commercialisation. 2. Examination of the regulatory framework governing clinical trials with advanced therapies (Chapter 3-6, Section 2): a. Responsible parties and tasks for clinical trial authorisation and supervision; b. Comparison of responsible parties with chemical-based medicines (i.e. whether the rules governing clinical trials for advanced therapies are different to those that apply to standard chemical-based medicinal products). 3. Examination of the regulatory framework governing the approval of advanced therapies (Chapter 3-6, Section 1, 3, 4): a. Scope of regulation (Chapter 3-6, Section 1): • Description of product classes regulated as advanced therapies; • Identification of classes not regulated as advanced therapies; • Description of methods to control advanced therapies without therapeutic indication. b. Comparison of approval procedures for advanced therapies with chemical-based medicines (Chapter 3-6, Section 3); c. Description of adaptive regulatory pathways for advanced therapies (Chapter 3-6, Section 3); d. Manufacturing and quality requirements for advanced therapies (Chapter 3-6, Section 4); e. Comparison of manufacturing and quality requirements between autologous/non autologous products (Chapter 3-6, Section 4); f. Regulation of incorporated medical devices (Chapter 3-6, Section 3); g. Possibility to rely on data other than clinical trials for demonstration of efficacy and safety (Chapter 3-6, Section 3); h. Other relevant aspects of regulatory framework for authorisation of advanced therapies (Chapter 3-6, Section 3). 4. Examination of post-marketing requirements for advanced therapies (Chapter 3-6, Section 4-5): a. Comparison of post-marketing requirements of advanced therapies with chemical-based medicines (Chapter 3-6, Section 5); b. Description of additional post-marketing requirements specific for advanced therapies (Chapter 3-6, Section 5); c. Description of processes of approval of changes in manufacturing processes of advanced therapies (Chapter 3-6, Section 4); d. Other relevant aspects of post-marketing requirements for advanced therapies. 5. Perceptions and views of stakeholders on the regulatory framework (Chapter 3-6, Section 7).

2.3.1. Desk research

We conducted desk research to retrieve and examine relevant official regulatory documents (e.g. legislation, guidelines), scientific publications and grey literature on the regulation of advanced therapies in selected jurisdictions. The data lock point was

31 December 2014. The search process for identification of relevant texts consisted of four steps.

Step 1: we identified official regulatory documents such as legislation, guidelines, presentations and reports from the websites of each of the four competent authorities. Key terms that covered various aspects of the regulatory framework were used to navigate the websites of competent authorities. Identified sources included plain text on websites, formal documents and PowerPoint or video presentations. Website searches relied largely on snowballing as official documentations often referred to other relevant documents created by the competent authorities.

Step 2: we applied a structured search strategy to relevant databases including PubMed, EMBASE and Web of Science to retrieve scientific publications. In these searches we used combinations of key terms describing the three elements of the study:

- Terms describing advanced therapies;
- Terms describing aspects of the regulatory framework;
- Terms describing the selected jurisdiction/country.

Step 3: we performed a free search in Google Scholar to retrieve grey literature, book chapters and additional scientific publications not indexed in relevant databases. Search terms were the same as those applied in the structured search, but were not necessarily combined in a single query. We also checked forward and backward citations of relevant documents in this step.

Documents that were identified in step 2 and 3 were included when they provided additional (to step 1) factual information on the regulatory framework on advanced therapies of the studied jurisdictions. Since regulatory frameworks and the advanced therapies field in general is rapidly evolving we gave priority in step 2-3 to recent (after 2012) publications.

Step 4: in some cases additional documentation such as presentations, concept papers or regulatory documents were obtained from stakeholders during in-depth interviews. These documents were also included as references in case they were deemed relevant.

In Annex 5 we provide all search terms and the inclusion criteria used for the structured search per jurisdiction.

2.3.2. In-depth interviews

We conducted semi-structured interviews with several stakeholders (see Annex 1 for details). The objective of the interviews was twofold: (1) obtain factual information about the regulatory framework (2) provide insight in views and perceptions of stakeholders on the functioning of this framework.

The semi-structured interviews consisted of five main topics and specific questions on these topics were tailored to each jurisdiction, the background of the interviewed stakeholder and knowledge gaps of the researchers on the regulatory framework. The semi-structured nature of the interviews also provided room for further discussion in case answers of the interviewees prompted additional questions. Additional information on interview content and conduct is provided in Annex 2.

An overview of interviews with stakeholders is provided in Annex 1.

2.4. Approach to the analysis of the economic aspects of the advanced therapies market

Our approach to analyse the economic aspects of the advanced therapies market in the selected jurisdictions included:

- Selection of authorised products for in-depth interviews in each jurisdiction;
- An analysis of the legal instruments, including an overview of:
  - relevant intellectual property rights (IPR) legislation;
  - incentives to support developers of advanced therapies (e.g. fee waiver);
  - the average approval procedure time; and
  - time to be commercialised after approval of selected products per jurisdiction.
- A quick scan on pricing and reimbursement policies that exists in the jurisdictions under study.

For this purpose, we conducted desk research (see Annex 9) and performed interviews with different stakeholders as presented in Annex 1.

2.4.1. Desk research

Part of the relevant information (on legislation) was retrieved for the analysis of the regulatory framework in each jurisdiction. Additional desk research was performed for the full analysis of relevant IPR legislation, incentives to support developers of advanced therapies, the average approval procedure time, time to be commercialised after approval, pricing, and reimbursement policies.

We used a structured search strategy to identify recent publications for all selected jurisdictions (see Annex 9). The desk research was used as input for in-depth interviews with relevant stakeholders in each jurisdiction.

2.4.2. Interviews

We conducted interviews (or had email correspondence) with representatives of bodies responsible for reimbursement/pricing of medicines, associations of developers of advanced therapies, entities that have obtained approval for the commercialisation of an advanced therapy, as well as innovation attaches. In addition, relevant competent authorities and patent offices in the jurisdictions concerned were contacted with regard to the relevant legislation about IPR.

In the interviews we focused on the economic aspects (targeted per relevant stakeholder) and – where relevant - on authorised products. In addition, we aimed to validate the research activities and the availability of advanced therapies (see section 2.2). The selection of the products for the interviews has been approved by the client and was based on the following selection criteria:

- (Type of) advanced therapies that are licensed in more than one country;
- When possible, we chose one cell based product and one tissue based product;
- When possible, we chose one allogeneic product and one autologous product;
- When only 1 or 2 advanced therapies have received approval in a jurisdiction, these were automatically included.

The selection included:

United States:

- TheraCys (biologic response modifier), this is the only approved biologic response modifier;
- Provenge (autologous cellular immune-therapy).

Canada:

- Prochymal (allogeneic bone marrow), as this is the only product with approval in Canada. Please note that Prochymal of Mesoblast/Osiris and TEMCELL of JCR Pharmaceuticals is exactly the same product. Prochymal is used in Canada and TEMCELL in Japan (based on an interview with a developer (US)).

Japan:

- JACC (autologous cultured cartilage, tissue based), one of the two products developed by J-TEC, both products are autologous and tissue based;
- HeartSheet (autologous skeletal myoblast sheet), one of the recent approved product in Japan.

South Korea:

- Cupistem (autologous adipose derived mesenchymal stem cells);
- Kaloderm (allogeneic keratinocytes), there are only two allogeneic products with approval in Korea. Kaloderm is similar to two other products in Korea, but the other two products are autologous keratinocyte products.

2.5. Synthesis and reporting

All information and (sub) conclusions were synthesised to reach a detailed description of available advanced therapies in the US, Canada, Japan and South Korea and the regulatory framework governing them. We have highlighted the specifics of each jurisdiction. It required factual information about a range of aspects linked to the regulation of advanced therapies in each country under study. The study also involved assessment of the state of play of the implementation of the regulation in each country – an assessment that can both be of objective character and of subjective character (and are likely to differ between stakeholders). The findings of this study are clearly based on evidence generated through the document review, literature review, and interviews with key stakeholders in the jurisdictions under study. We provided extensive references to the relevant regulatory provisions and sources of information used.

2.6. Peer review

The work was subject to review of several interviewees and Commission officials. In addition, an internal quality check was undertaken by two senior experts in the field which were not involved in the execution of the research (Professor Leufkens, Utrecht University and Dr Goettsch, National Health Care Institute in the Netherlands).

3. Analysis of the regulatory framework governing advanced therapies in the United States

3.1. Overview of regulatory framework for advanced therapies in the US

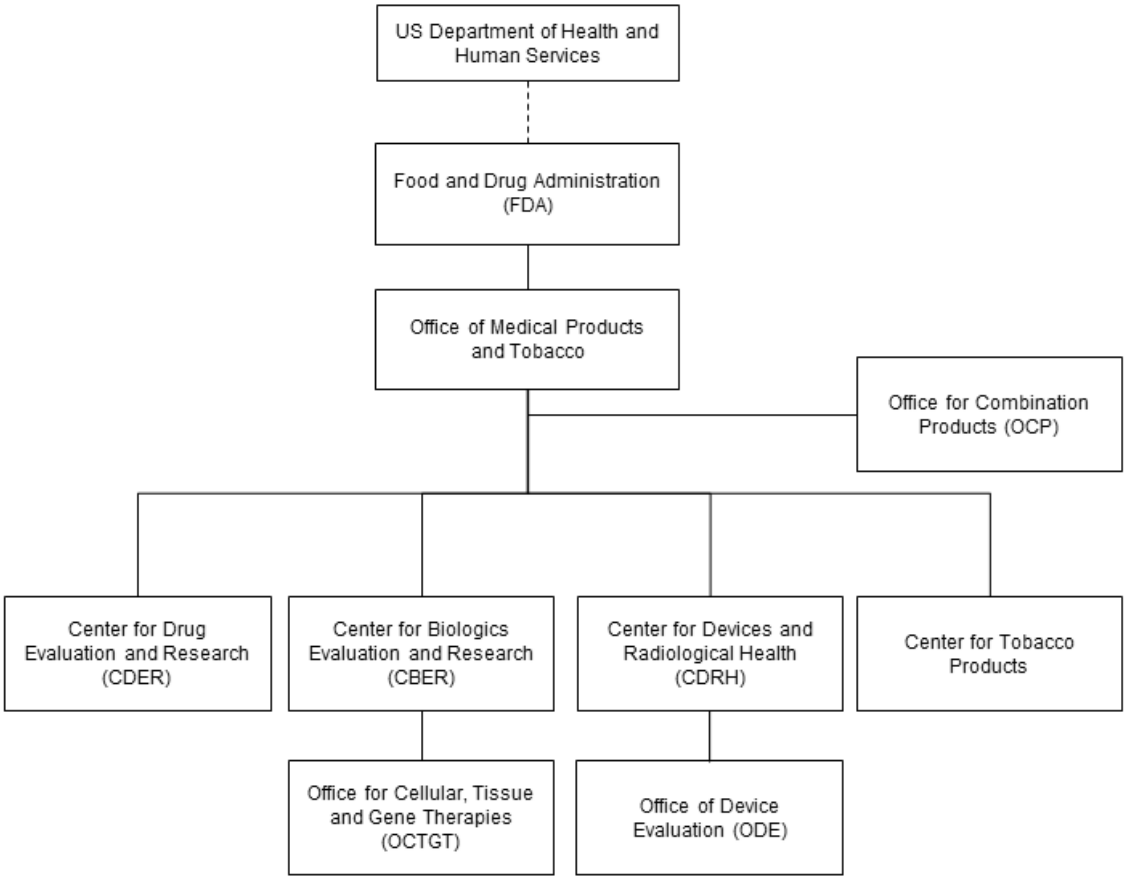
3.1.1. Regulatory responsibilities and mandate

The Food and Drug Administration (FDA) is the federal regulatory agency in the United States (US). The mission of the agency is to protect and promote public health through the regulation of a wide range including medicinal products such as chemical-based drugs, biologic products and medical devices. Responsibilities with respect to medicinal products include assessment and authorisation of clinical trials (section 3.2) and marketing approval for medical products (section 3.3).

Within the agency, responsibilities for *drugs*, *biologic products* and *devices* are organised in separate centres; (-) the Centre for Drug Evaluation and Research (CDER) has oversight over chemical-based *drugs* but also some biotechnology products, including monoclonal antibodies and cytokines, (-) the Centre for Biologics Evaluation and Research (CBER) has oversight over vaccines, blood products, and advanced therapies, and (-) the Centre for Devices and Radiological Health (CDRH) regulates *devices*.[1]

All of these centres are supported by dedicated offices that oversee regulation of particular product categories. Regulation of advanced therapies is the primary responsibility of the Office for Cellular, Tissue and Gene Therapies (OCTGT).[2] Besides advanced therapies, the OCTGT regulates a wide variety of other products such as tumour vaccines, xenotransplantation and *biologic product-device* combination products. The Office of Device Evaluation oversees the approval of medical *devices* on the market. Figure 3.1 gives an overview of the main centres and offices involved in the regulation of medicinal products including advanced therapies.

Figure 3.1 Overview of Centres and Offices of the Food and Drug Administration



3.1.2. Description of general regulatory framework

The US federal regulatory framework consists of a) statutes passed by the Congress and signed into law by the President; b) regulations that provide details on interpretation of laws and are implemented by the FDA; and c) non-binding guidelines reflecting FDA's current thinking on development and on ways to comply with the regulatory requirements in the day-to-day activities of FDA staff and developers.

Two statutes are particularly relevant to the regulation of advanced therapies as defined in this report: the Public Health Services Act (PHSA)[3] and the Food, Drug & Cosmetics Act (FDCA).[4] The statutes provide the FDA with the legal authority to regulate human medicinal products as *drugs, biologic products or devices.* They also define these product types and provide responsibilities in regulating them.[5]

Title 21 of the Code of Federal Regulations (CFR) provides details on how FDA implements the activities that are defined in the PHSA and FDCA and other relevant statutes. The parts of CFR that are relevant for the regulation of *drugs, biologic products and devices*, respectively, are CFR part 200-299 and 300-369 for *drugs*, CFR parts 200-299 and 600-680 for *biologic products* and CFR parts 800-898 for medical *devices*. More details and a summary of the most important CFR parts referred in this chapter are provided in Table 3.1.

Table 3.1 Main statutes and regulations that are applicable for medical products

Product type	Statutes	Code of Federal Regulations
Drug	FDCA	200-299; 300-369
Biologic product	FDCA, PHSA	200-299; 312; 600-680
Device	FDCA	800-898
HCT/Ps	PHSA	1271
General regulations	FDCA	4 (combination products)
		50 (protection human subjects)
		54 (financial disclosure)
		56 (IRB)
		58 (GLP)

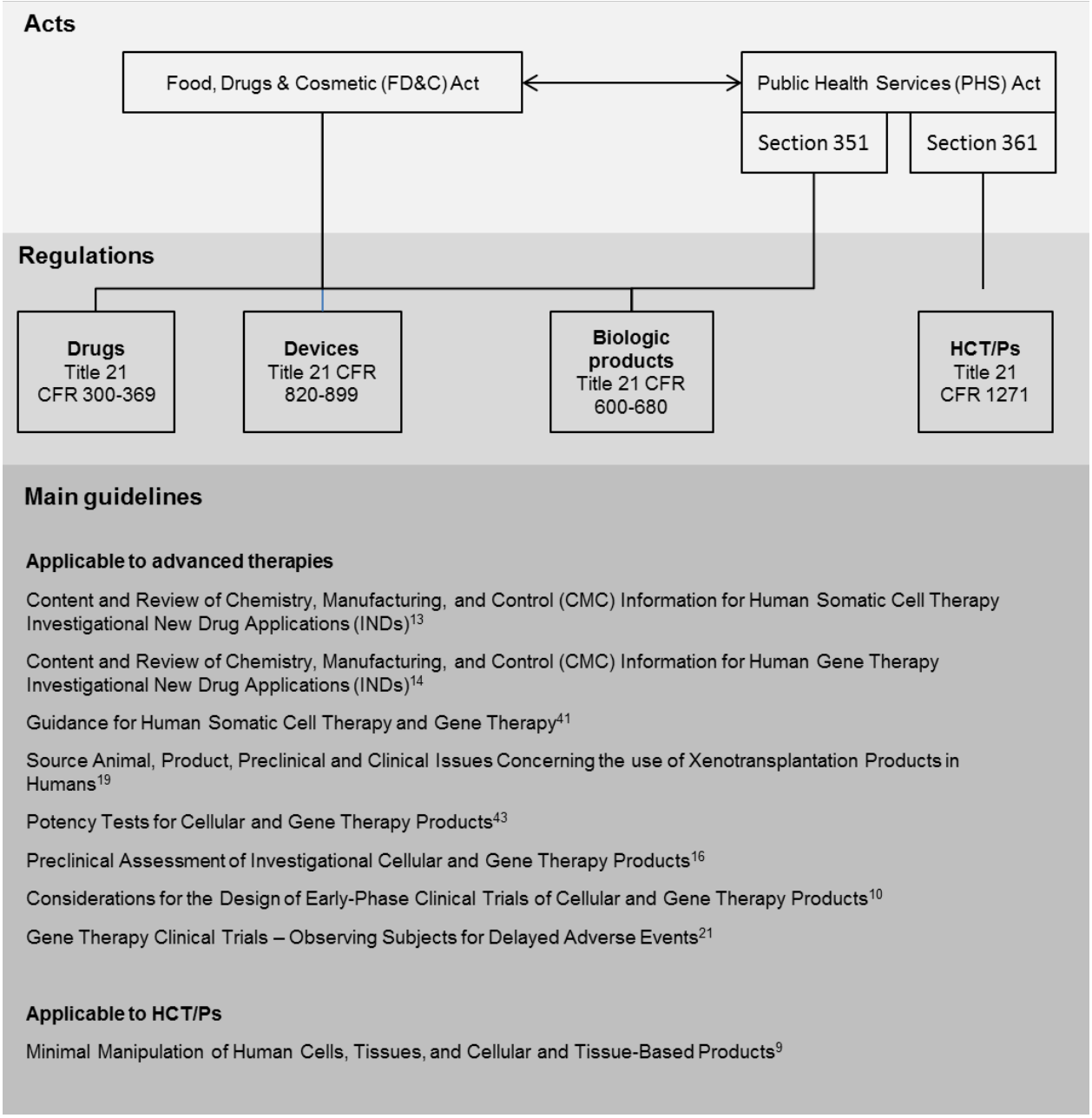
FDCA = Food, Drug and Cosmetics Act; PHSA = Public Health Services Act.

Guidance documents facilitate both FDA staff and industry in the appropriate interpretation of statutes and regulations. They are not legally binding. Guidance documents may focus on a particular regulatory activity (e.g. submission of clinical trial dossier), indication or product type.

Other means by which the FDA interacts with key stakeholders in the advanced therapy field to improve efficiency of processes and product development include consultation meetings, interagency cooperation, and specific advisory committees, among others.[6]

Figure 3.2 provides a schematic overview of the regulatory framework in the US particularly those Statutes, Regulations and Guidance documents which bear relevance for the regulation of advanced therapies and are discussed in this chapter.

Figure 3.2 Overview of statutes, regulations, and guidance documents for medical products



3.1.3. Regulatory framework for advanced therapies

Advanced therapies are regulated as biologic products. GCT-based products that are more-than-minimally manipulated, or for non-homologous use, or have a systemic effect or depend on its metabolic activity (except for autologous cells, allogeneic cells for 1st of 2nd degree relatives and reproductive cells) are regulated as biologic products. This definition of GCT-based products that are regulated as biologic products in the US is broader than the definition of advanced therapies. For example, unrelated allogeneic hematopoietic stem/progenitor cells are regulated as biologic products due to systemic effects,[7] but this class does not adhere to the definition of advanced therapy.

Table 3.2 Product definitions

Product type	Definition
Drug (FDCA, section 201 (h), 21 U.S.C. 321 (g)(1))	(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343 (r)(1)(B) and 343 (r)(3) of this title or sections 343 (r)(1)(B) and 343 (r)(5)(D) of this title, is made in accordance with the requirements of section 343 (r) of this title is not a drug solely because the label or the labelling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343 (r)(6) of this title is not a drug under clause (C) solely because the label or the labelling contains such a statement.
Biologic product (PHSA, section 351(i) 42 U.S.C. 262(i))	A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.
Human cell, tissue and cellular and tissue-based products (HCT/P) (21 CFR 1271.3(d))	Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.
Device (FDCA, section 201 (h), 21 U.S.C. 321(h))	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is— (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.”

Adapted from Bailey et al. 2015.[15] FDCA = Food, Drug and Cosmetics Act; PHSA = Public Health Services Act.

Guidelines for GCT-based products that are regulated as biologic products refer to these products as human somatic cell therapy and human gene therapy (see Figure 3.3). From here on these products are referred to as 351 GCT-based (see next paragraph for reason) although they are not defined in the legislation or in the guidelines as such. Legal definitions of the general product categories are provided in Table 3.2.

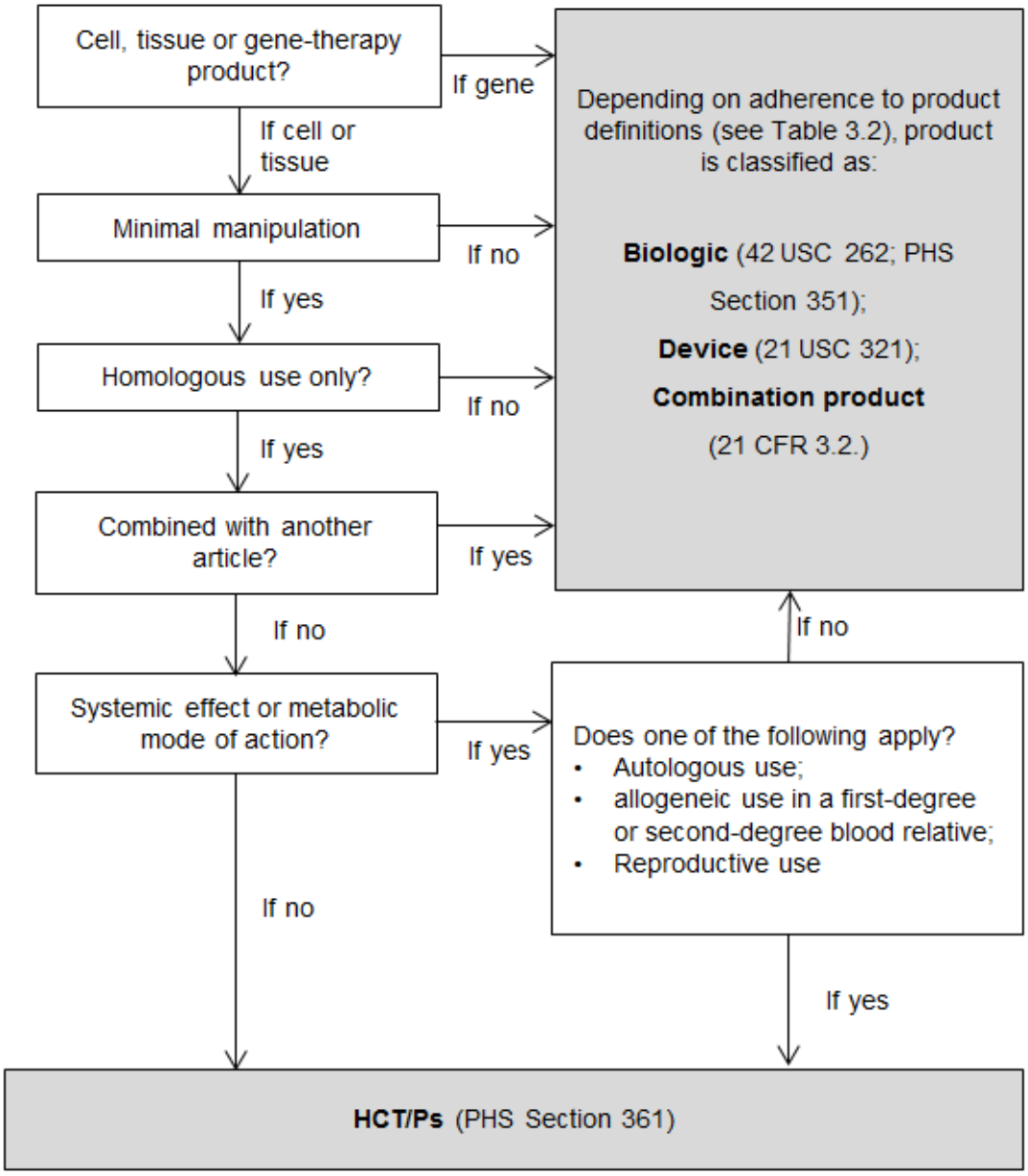
Section 351 and Section 361 of the PHSA are of relevance to determine whether GCT-based products need to obtain a license for commercialisation before they can be administered to patients. Section 351 defines and regulates *biologic products* and mandates that a license is necessary for their commercialisation. A standard license for a *biologic product* requires quality, safety and efficacy data from confirmatory clinical trials, which is the same requirement as for a standard license for chemical-based drugs (see section 3.3). Section 361 mentions the development and enforcement of regulations to prevent the introduction, transmission, or spread of communicable diseases.[8]

GCT-based products may also be a combination of a *biologic product* and a *device* which is referred to as a combination product. The Office of Combination Products (OCP) is responsible for handling Requests for Designations (RFDs) of combination products to determine the responsible Office within the FDA and the regulations that apply. Designation of combination products is based on the primary mode of action of the product.

Several guidelines are in place that further specify standards for development and authorisation of 351 GCT-based products. These guidelines provide guidance to sponsors with respect to manufacturing and quality requirements, preclinical studies and clinical studies, among others. An overview of guidelines that are relevant for this report are listed in Figure 3.3.

Figure 3.3 provides an overview of how the general class of GCT-based products is sub-categorized in the US regulatory framework as a *biologic product* or *HCT/P*. Specific definitions that are of relevance for *HCT/Ps* are provided in section 3.1.4.

Figure 3.3 Classification of GCT-based products



3.1.4. Products exempted from the requirements to obtain marketing authorisation

The subset of products regulated as *HCT/Ps* are exempt from obtaining a marketing authorisation.[9] They are regulated through 21 CFR 1271. *HCT/Ps* include autologous cells and allogeneic cells for 1st of 2nd degree relatives and reproductive cells that have a systemic effect or depend on their metabolic activity for its primary function, but these are minimally manipulated and for homologous use.[9]

The regulations for *HCT/Ps* are primarily in place to prevent the spread of communicable diseases when products are intended for implantation, transplantation, infusion, or transfer into a human recipient (21 CFR 1271.3(d)). *HCT/Ps* are classified according to the standards set out in 21 CFR 1271.10(a)(1). The criteria for considering a product as a HCT/Ps are mentioned in 21 CFR 1271.10 and listed below:

"1) The HCT/P is minimally manipulated;
2) The HCT/P is intended for homologous use only, as reflected by the labelling, advertising, or other indications of the manufacturer's objective intent;
3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4) Either:
i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function; and:
a) Is for autologous use;
b) Is for allogeneic use in a first-degree or second-degree blood relative; or
c) Is for reproductive use."

Under 21 CFR 1271.3(f), minimal manipulation is defined as:

"1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement;
2) For cells or non-structural tissues, processing that does not alter the relevant biological characteristics of cells or tissues."

Several requirements are in place to regulate these therapies. These include donor eligibility and testing (21 CFR 1271.45-90), registration of manufacturing establishments and product listings (21 CFR 1271.21-37), and compliance with current Good Tissue Practice (GTP) (21 CFR 1271.150-320). For HCT/Ps adverse reactions need to be monitored and reported under 21 CFR 1271.350, but there are no additional clinical requirements.

21 CFR 1271 which regulates HCT/Ps is not applicable to some product types that also do not fall under the definition of biologic product. These product types may be regulated by other Statutes or Regulations that fall either within or outside the jurisdiction of the FDA. Specific product categories are:[9]

"1) Vascularized human organs for transplantation;
2) Whole blood or blood components or blood derivative products subject to listing under 21 CFR Parts 607 and 207, respectively;
3) Secreted or extracted human products, such as milk, collagen, and cell factors, except that semen is considered an HCT/P;
4) Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow);
5) Ancillary products used in the manufacture of HCT/P;
6) Cells, tissues, and organs derived from animals other than humans;
7) In vitro diagnostic products as defined in 21 CFR 809.3(a); and

8) Blood vessels recovered with an organ, as defined in 42 CFR 121.2 that are intended for use in organ transplantation and labelled "For use in organ transplantation only." (21 CFR 1271.3(d))"

3.1.5. Description of methods to control advanced therapies without therapeutic indication

Cosmetics fall under the jurisdiction of the FDA and are regulated under the FDCA and 21 CFR 700-740. Cosmetics are defined as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance" (FDCA, section 201(i)). Products that fall under these sections do not need to obtain authorisation for marketing. However, the FDA indicated that if therapeutic claims are made with cosmetic products that contain cellular components, these products may meet the definition of *drug or biologic product*. If the cellular components are viable, the cosmetic product meets the definition of *biologic product*. If the cellular components are non-viable, the cosmetic product meets the definition of *drug*. Depending on specific product characteristics, a component of the product may also adhere to the definition of *device*. More information on combination products can be found in section 3.3.3.

3.2. Framework governing clinical trials with advanced therapies

3.2.1. Responsible parties and tasks for clinical trial authorisation and supervision

Investigational use of *drugs* and *biologic products* is regulated by the FDA. Before sponsors can sell or distribute these products, they need to file an Investigation New Drug (IND) application for both *drugs* or *biologic products* (21 CFR 312). The procedures and requirements for *biologic products* are outlined below. All phase clinical trials are authorized by institutional review boards (IRB) and protocols for next phase studies have to be submitted to the FDA.

Clinical trial authorisation of 351 GCT-based products

Advanced therapies are regulated under section 351 of the PHSA and developers need to apply for an IND under the authority of the OCTGT.[10] Regulations for an IND are the same for chemical-based *drugs* and *biologic products*, including advanced therapies (21 CFR 312). However, not all standards may be applicable or suitable for advanced therapies. To clarify this situation, there are several means by which the FDA provides guidance to sponsors, including guidance documents and meetings with the OCTGT. Below more details are provided on the regulations for INDs that are applicable to chemical-based *drugs* and *biologic products,* and specific guidance that is provided for advanced therapies.

Requirements for an IND are defined in regulation 21 CFR 312.23(a). Mandatory elements include provision of a: (1) general investigational plan; (2) an Investigator Brochure (except when the study is conducted by an investigator); (3) product/chemistry, manufacturing, and control (CMC) information; (4) pharmacology/toxicology information; (5) previous human experience information (6) and clinical protocol and informed consent.[11] In the following paragraphs we will discuss IND expectations in detail, especially with regard to CMC, pharmacology and toxicology and clinical protocols. Where available we will refer to the requirements that are specifically in place for advanced therapies.

The CMC section of an IND typically covers details on the 1) drug substance (active component), 2) drug product, 3) placebo formulation (if applicable, 4) labelling and 5) environmental assessment. For the drug substance and drug product, all relevant manufacturing and testing information has to be included in the IND. This includes the method of preparation, plus the test methods and acceptable limits for product characterization.[12]

To meet specific manufacturing challenges for advanced therapies regulated under PHSA Section 351, the OCTGT provides specific guidance on the CMC section to be included in an IND for human somatic cell therapies: *Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)*;[13] and for human gene therapies: *Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*.[14] For an IND of these two product categories to be authorized, it is expected that 1) comparability of product characterization and biologic activity that was used to generate preclinical data can be demonstrated, and that 2) safety in humans is plausible.[15] The FDA uses a flexible approach for manufacturing and quality requirements in early-stage development, which becomes more stringent as development progresses. The allowed flexibility in meeting specific manufacturing and quality requirements for advanced therapies is further discussed in section 3.4.

General preclinical pharmacology and toxicology standards for *biologic products* under 21 CFR 312 are also applicable to advanced therapies regulated under section 351. 21 CFR 312.23(a)(8), which is applicable to all INDs, states that "*[a]adequate information about the pharmacological and toxicological studies…on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required vary with the duration and nature of the proposed clinical investigations*." Thus, determination of the preclinical pharmacology and toxicology studies that are required for an IND is done on a case-by-case basis for *biologic products*, including advanced therapies that are regulated as such.

Sections on pharmacology and toxicology for an IND for chemical-based *drugs* or *biologic products* typically cover information on *in-vitro* and *in-vivo* animal data that can support the initial safe dose for use of the product in humans.[16] A proof of concept using *in-vivo* animal models is required if a suitable animal model is available. Furthermore, toxicology studies and complete study reports need to be included in an IND (21 CFR 312). Safety monitoring plans need to include study stopping rules that are regulated under 21 CFR 312.32.[5] Under 21 CFR 58, all preclinical studies need to be conducted according to Good Laboratory Practice (GLP). For 351 GCT-based products some studies may be exempt from this rule, depending on whether facilities that are needed for specific animal studies are available in a GLP facility.[16]

Specific product characteristics of advanced therapies may impose scientific challenges while trying to adhere to the IND requirements. Non-existing knowledge of previous exposure to humans, difficulties in the determination of dose and regimen from animal data, scale of manufacturing, and other factors affect the clinical trial design.[16] To meet these scientific challenges the OCTGT provides guidance for preclinical studies with advanced therapies: *Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products*.[16] This document provides guidance for the design of proof-of-concept studies, selection of animal models, toxicology studies and product delivery considerations. It also outlines specific recommendations for cell therapy versus gene therapy products, for example

recommendations how to study engraftment and vector considerations, respectively. Ultimately, preclinical studies of advanced therapies need to support 1) establishment of biological plausibility, 2) identification of active dose levels, 3) selection of starting dose, dose-escalation scheme, and dosing regimen to be used in clinical studies, 4) safety and feasibility of the proposed route of administration in clinical studies, 5) patient eligibility criteria, 6) physiologic parameters to be used for clinical monitoring, and 7) identification of public health risks.[16]

A thorough risk-benefit analysis that is science-driven, taking into account the unique biological properties and the intended clinical indication, is performed by the OCTGT in the evaluation of preclinical data of advanced therapies. Safety of advanced therapies needs to be assessed through toxicology studies that originate from animal studies or previous clinical experience with similar products or mode of delivery.[16] Key considerations for assessing risk of advanced therapies includes tumourigenicity, and immunogenicity, plus undesirable modification of genetic material.[17] Products that are of xenogeneic origin pose additional risk for the host and public health due to possible transmission of infectious agents,[18] immunological responses by the host, and enhanced tumourigenicity of xenogeneic products.[19] It is also highlighted that additional preclinical studies can be required if the product characteristics of advanced therapies change later on in development (clinical studies).[16] This approach to changes in manufacturing of advanced therapies was confirmed by a US developer of advanced therapies.

For the IND application of advanced therapies, the clinical protocol section should include the study design and statistical methods, endpoints, preclinical data, follow-up studies, and data on previous human exposure.[2] These should provide a scientific rationale for the clinical trial approach, including a safe starting dose and dosing-escalation scheme and dosing regimen, eligibility of study population, monitoring strategies and identify potential local or systemic toxicities.[20]

To address scientific challenges of the design of early-phase (I & II) clinical trials with advanced therapies, OCTGT provides guidance: *Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products*.[10] In the document specific issues that developers of advanced therapies may encounter are highlighted, such as choosing the appropriate study population, the use of control groups, dose determination, and altered treatment plans such as staggered approaches. Guidance is also provided for monitoring in order to capture product specific safety concerns, such as infusion reactions, graft-versus-host-disease, and undesired immunological and tumourigenic reactions.[10] Follow up monitoring of patients that were treated with advanced therapies may need to be long term due to possible delayed effects, in particular for gene therapy products.[21] In addition, other additional aspects that are relevant for advanced therapies may be incorporated into the clinical trial design, such as the feasibility of administration and pharmacologic activity in humans.

Before IND submission for advanced therapies there are formal pre-IND meetings with the OCTGT that are mandatory to optimize the IND submission process. Developers of 351 GCT-based products also have formal meetings with the OCTGT after completion of phase I and phase II studies to ensure that the design of the trials enables evaluation of effectiveness and safety in the context of a biologics license application.[22] It is the responsibility of the IRB to authorize all clinical trials (21 CFR 56.103(a)). In addition, the FDA evaluates late phase II and III clinical trial protocols separately from the initial IND application, which need to be submitted by developers after discussing results of early phase clinical trials in meetings with the FDA. The OCTGT also encourages pre-pre-IND meetings with developers to engage in discussion

in an early stage to streamline research and development as much as possible.[11] These meetings are informal and the feedback is not binding for future submissions.[23]

The FDA published the ICH E6 Good Clinical Practice (GCP) guideline in the Federal Register in 1997.[24] Many sections of the FDA regulations incorporate aspects of the latest GCP guideline, including 21 CFR 50, 56, 210, 312, 314, 320, 812, 814).[25] The IND application needs to include a GCP compliance certificate.[2] Once an IND is approved, all general regulations for conduct of clinical trials that are applicable to *drugs* and *biologic products* also apply to advanced therapies[5] (e.g. protection of human subjects, informed consent, 21 CRF part 50; financial disclosure by clinical investigators; 21 CFR part 54; approval by an IRB; 21 CRF part 56).[26] All clinical trials also have to be reviewed and approved by an IRB before the trial can be initiated. The IND needs to include a commitment of the sponsor that ensures approval by an IRB for all proposed clinical trials (21 CFR 312.23 (a)(iv)).

3.3. Framework governing commercialisation of advanced therapies

3.3.1. Approval procedures for advanced therapies vs. chemical-based medicines

Sponsors of 351 GCT-based products including advanced therapies need to submit a Biologics License Application (BLA), as described in the next section.

The regulations for licensing procedures for chemical-based drugs can be found under 21 CFR part 314. The specific sections that need to be included in a New Drug Application (NDA) are specified under 21 CFR 314.50. Technical sections include a chemistry, manufacturing, and controls (CMC) section, non-clinical pharmacology and toxicology section, and a clinical section.

Approval procedures for 351 GCT-based products

For 351 GCT-based products developers need to apply for a BLA under the authority of the OCTGT.[10] The same general regulations apply to all BLAs, but specific guidance is provided as to how to interpret these regulations for advanced therapies. In the following we first describe the general provisions and review procedures for BLAs, followed by specific information for advanced therapies, where available.

Biologics licensing is regulated under 21 CFR 601. The main purpose of a biological license is to demonstrate safety and efficacy of biological products and provide correct labelling based on CMC information, preclinical and clinical data, among others (21 CFR 601.25). The FDA recently made it obligatory to submit all NDAs, certain BLAs and INDs, and abbreviated NDAs in an electronic form that is structured according to the CTD of the ICH.[27]

General provisions for filing a BLA for all *biologic products* are specified under 21 CFR 601.2. Preclinical studies need to comply with Good Laboratory Practice (GLP) (21 CFR 58); clinical studies need to comply with Institutional Review Board (IRB) authorisation procedures (21 CFR 56) and human protection measures of informed consent (21 CFR 50). Other general provisions include details of manufacturing methods and evidence of stability. Samples representing lots need to be provided with corresponding quality test results. Specimens of labels, enclosures, containers and potentially a Medication Guide (21 CFR 208) need to be enclosed, and addresses of each manufacturing site of the biologic product needs to be included in a submission for the CBER to take it into consideration (21 CFR 601.2).

Not all sections that are part of a BLA will be applicable to advanced therapies because of the lack of pharmacokinetic studies and complex pharmacodynamics compared to *biologic products* such as monoclonal antibodies and cytokines. These scientific challenges demand a flexible approach in determining which requirements for a BLA are plausible.[15] The OCTGT provides specific guidance for advanced therapies as to how to build the information from preclinical studies for the application of an IND and BLA,[16] and how to design early-phase clinical trials with advanced therapies.[10] Specifics of these guidelines are discussed in more detail in section 3.2.1.

The CMC section of a BLA for advanced therapies also requires a flexible approach because of their unique product characteristics. In addition, the requirements for the CMC section become more stringent as advanced therapies progress to more advanced stages of product development. The OCTGT published documents for human somatic cell therapies[13] and human gene therapies[14] that provide guidance on CMC. A US developer indicated that it is determined on a case-by-case basis on which quality control tests and product specifications a BLA is granted. These requirements are likely to differ per product. BLA requirements that are specifically mentioned in the guidance documents for advanced therapies are 1) stability assessments of the end of production cells obtained from a master cell bank, 2) polymerase chain reaction (PCR) assays for mycoplasma, and 3) final product stability testing.[13,14] Relevant parts of these guidelines for the BLA procedure are discussed in section 3.4 (manufacturing and quality).

The FDA has indicated that it evaluates the submitted scientific evidence on a case-by-case basis to determine whether the risks outweigh the potential benefits and to consequently grant a biologic license for advanced therapies. As it may be very difficult to predict all risks and benefits of advanced therapies, risk can be mitigated with detailed product characterization and adequate preclinical evidence.[23] Moreover, certain post-marketing requirements may be imposed upon sponsors to further reduce uncertainties in the post-marketing phase (see section 5).

3.3.2. Schemes to facilitate early approval

There are four regulatory pathways in place that offer potential faster availability of chemical-based *drugs* or *biologic products*; priority review, breakthrough therapy, accelerated approval, and fast track approvals.[1] In case a product adheres to the eligibility criteria, developers of advanced therapies could request use of these pathways or FDA staff may decide on their discretion to use the pathway. These four pathways including their eligibility criteria and advantages for the sponsor pathway are summarized in Table 3.3.[28]

Table 3.3 Description of alternative regulatory pathways available for advanced therapies

Regulatory pathway	Eligibility criteria	Benefits
Fast Track	Drugs that treat serious conditions and fill an unmet medical need: No other treatment is available; superior efficacy, avoiding serious adverse drug reactions, or improving diagnosis, decreasing toxicity over current treatment, or address a public health need.	More frequent meetings and written communication with the FDA Eligibility for Accelerated Approval and Priority Review Rolling review (staggered submission)
Breakthrough Therapy	Drugs that are intended to treat a serious condition and preliminary clinical results demonstrate indications of substantial improvement over available therapy. Request should in general not be made later than the end-of-phase-2 meeting.	All benefits of Fast Track Intensive guidance from phase 1 onwards Organisational commitment involving senior managers
Accelerated Approval	Approval for drugs based on surrogate endpoints that are intended to treat a serious condition for which there is an unmet medical need.	Accelerated clinical development Confirmatory studies post-marketing
Priority Review	Drugs that show significant improvements in the safety or efficacy of the treatment, diagnosis, or prevention of serious conditions.	Review within 6 months (instead of 10 months) Standards for evaluation unaltered

Unmet need is defined as: "providing a therapy where none exists or providing a therapy which may be potentially better than available therapy." [28]

3.3.3. Regulation of incorporated medical devices

Combination products are designated to a specific Centre within the FDA for oversight based on the primary mode of action of the product. If sponsors are uncertain which centre is applicable to their product, they can enter a Request for Designation (RFD) at the Office of Combination Products (OCP). The OCP has overarching oversight on combination products, in addition to the centre to which the product is allocated based on the primary mode of action.[1] Primary mode of action is defined under 21 CFR 3.2(m):

"the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product."

Generally, one marketing authorisation procedure is sufficient for combination products. In some cases, it is necessary to enter two marketing authorisation procedures at both Centres that are assigned to the product, for example when different parts of the product have already been approved and labelling needs to be updated.[29] A draft guidance on how to classify combination products was published in 2011 for comments by the public.[30] To date, the guidance document has not been finalized and sponsors are encouraged to contact the OCP for a RDF procedure in case of uncertainties. Combination products are defined under 21 CFR 3.2:

> "1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
> 2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
> 3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labelling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
> 4) Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect."

3.3.4. Possibility to rely on data other than clinical trials for demonstration of efficacy and safety

The Animal Rule allows approval of *drugs* (21 CFR 314.600) and *biologic products* (21 CFR 601.90), only if definite human efficacy clinical studies are not ethical or not feasible. The FDA relies on animal studies under the Animal Rule, which need to prove to be a reliable indicator of efficacy in humans. The criteria to determine the predictive efficacy in humans are 1) an understanding of pathophysiological mechanism of toxicity, 2) demonstration of efficacy in multiple animal species, unless an animal model is used that is validated for responses in humans, 3) the endpoint in animal studies is directly related to the desired human clinical benefit, 4) pharmacokinetics and pharmacodynamics of the product in animals allows to select an effective dose for humans.[31] If preclinical studies of advanced therapies adhere to these criteria, they are eligible for approval under the Animal Rule. However, so far this rule has not been used in case of advanced therapies. The FDA has applied the Animal Rule to approve a few products, including moxifloxacin for treatment of plague[32] and raxibacumab for treatment of inhalational anthrax.[33] To date, the Animal Rule has not been used for approval of 351 GCT-based products.

In case of emergencies, unapproved chemical-based drugs and biologic products may be authorized an Emergency Use Authorisation (EUA).[34] The Secretary of Health and Human Services may authorize an EUA under section 564 of the FDCA under the following circumstances:

> "1) a determination by the Secretary of Homeland Security that there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a specified biological, chemical, radiological, or nuclear agent or agents;
> 2) a determination by the Secretary of Defence that there is a military emergency, or a significant potential for a military emergency, involving a heightened risk to United States military forces of attack with a specified biological, chemical, radiological, or nuclear agent or agents; or
> 3) a determination by the Secretary of a public health emergency under section 319 of the Public Health Service Act (PHS Act) that affects, or has the significant potential to affect, national security, and that involves a specified biological, chemical, radiological, or nuclear agent or agents, or a specified disease or condition that may be attributable to such agent or agents" (FDCA, Section 564(b)(1)).

Case study reports that may originate from the Expanded Access Program (see section 3.6) or other treatment can be submitted as part of a BLA, indicated by form FDA 356h.

3.4. Manufacturing and quality requirements for advanced therapies

In this section manufacturing and quality regulations that are specific for 351 GCT-based products are discussed, as well as general manufacturing and quality regulations for *biological products* if these are applicable to 351 GCT-based products. Some *HCT/Ps* regulations that also apply to 351 GCT-based products are also discussed. FDA's current approach to the regulation of 351 GCT-based products takes into account the diversity and complexity of these products. The FDA assesses manufacturing and quality requirements for 351 GCT-based products on a case-by-case basis, depending on how these products are derived, the phase of product development, state of scientific knowledge and regulatory precedents and experience with the product and its indication.[15] For all investigational products, the FDA exempts Phase I trials from full compliance with Good Manufacturing Practice (GMP) (section 3.4.5).[35]

General GMP regulations are applicable to all *drugs* and *biologic products* (21 CFR 210-211). For *biologic products*, additional regulations under 21 CFR 600, 606, and 820 are applicable (21 CFR 601.2). Testing is required to confirm potency, sterility, purity, and identity upon BLA approval.[36] These manufacturing and quality requirements are also applicable to advanced therapies.[37] Developers indicated that it can occur that not all mentioned types of assays are part of the quality control procedures for 351 GCT-based products due to remaining scientific challenges. Developers indicated that collaboration with the OCTGT is essential to determine what is feasible and acceptable for a particular therapy.

The FDA has issued specific guidance documents for preparation (by sponsors) and assessment (by regulators) of the content and review of CMC sections in IND applications for both human somatic cell therapies[13] and human gene therapies.[14] There is overlap between these documents, but the guideline on manufacturing and

testing for *human gene therapies* provides additional guidance on vectors.[11] In the following sections, we will specifically mention whether CMC requirements apply to human somatic cell therapies, human gene therapies, or both.

After the initiation of clinical trials, it is expected that knowledge on manufacturing, release, stability, distribution, and compliance with GMP increases to the level of full compliance with CMC requirements for a BLA (section 3.3.1). Prior to release on the market, products need to be tested for safety, quality, and consistency according to the approved manufacturing and quality standards in the BLA. The exact testing methods will be product-specific, but suitable measures of sterility, contamination, purity, potency, identity and product characterization need to be captured in manufacturing and testing protocols throughout product processing stages.[15] The regulations and guidance for manufacturing and quality of 351 GCT-based products are discussed in the next sections.

3.4.1. Starting materials

Regulations for starting material are similar for 351 GCT-based products and *HCT/Ps*, and can be found under 21 CFR 1271.45-90. As the risk of transmission of infectious diseases is a main concern when using starting materials of biologic origin, donor screening and testing of products when using allogeneic cells is obligatory.[11] Donors medical history and donor material needs to be tested for a set of pathogens, including HIV and hepatitis B and C. Use of diagnostic kits that are licensed by the FDA are mandatory for these tests.[13]

Donor screening and testing of autologous cells is not obligatory (21 CFR 1271.90(a)(1)).[11,13] The methods used for recovery/collection, list of facilities, and transport details do need to be provided in the IND for autologous cells. If any cell-based starting material originates from cell banks, testing is required to establish that cells are free from pathogens, cells are identified, cells are not contaminated with other cells, and they have the desired activity, among others.[13]

For human gene therapies, additional information needs to be provided on the vector that carries the gene. Specific information that needs to be documented is a gene map of the vector and the gene(s) to be inserted in the patient, and all relevant genetic regulatory elements that are involved in the transcription of the genes to be inserted. A vector diagram and genetic sequence analysis need to be documented as well. Further details on this can be found in the CMC guidance document for human gene therapies.[14]

3.4.2. Active substances

Active substance often correlates with starting materials and the final product for advanced therapies. Therefore, requirements for active substance are described throughout section 3.4 (section 3.4.1, 3.4.4, 3.4.5).

A combination product may also contain a chemical substance (instead of a *device* as explained in section 3.3.3) in addition to the biologic component that makes the product an advanced therapy. If it concerns a chemical substance for which previous submissions of CMC information have been approved, new submission of this information is not required. It does need to be clear to the CBER that the chemical substance was previously authorized. CBER staff needs to consult with the CDER if the proposed manufacturing and/or quality procedures raises any concerns.[13,14] A developer indicated that combination use of a drug with a 351 GCT-based product requires direct engagement with the CDER.

3.4.3. Excipients

All components that are used for drug manufacturing need to be listed in an IND, including excipients and processing aids (21 CFR 312.23(a)(7)(iv)(b)). For advanced therapies, all reagents or other processing aids that are used for cell manufacturing, but that are not part of the final product, need to be listed in the IND (e.g. used for cellular growth, differentiation, and purification). Excipients that are part of the final product (e.g. human serum albumin) need to be qualified for use in humans (21 CFR 211.84(a)), and listed in the IND. Furthermore, all manufacturing processes in which these reagents, processing aids, and excipients were used need to be described in the IND in order for the CBER to evaluate identity, quality, purity, and potency of the advanced therapy.[13,14]

3.4.4. Processing aids and product characterization

Product testing protocols need to be satisfactory at the point of BLA approval. Subsequently, these protocols are used prior to lot release to test the safety, quality, and product characterization for consistency purposes. For 351 GCT-based products, typical characterization tests measure biochemical, biophysical, or genetic properties. Specific examples include measures transduction completion of the vector for human gene therapies, and morphology for *cell therapy products*.[15] However, the most suitable testing assays may be different for each advanced therapy. For example, diverse characterization methods for mesenchymal stem cells-based investigational products have been submitted to the FDA.[38] In response to the diversity between advanced therapies, the FDA uses a flexible approach in the evaluation of any sections that involve assays.[37]

Identity assays are required for quality testing procedures. For *human gene therapies* it is recommended to identify both the vector and the cellular component of the product.[14] For *human cell therapies* identify assays that measure cell surface proteins can be used for example.[13] Identity assays are an essential part of the CMC information that inform product quality.[15]

3.4.5. Manufacturing

GMP

The FDA mandates that all manufacturing of *drugs* and *biologic products* need to comply with current Good Manufacturing Practice (cGMP) under 21 U.S.C. 351.[11] Section 21 CFR 210.2 specifies how these requirements are applicable to *biologic products* (including advanced therapies) and *HCT/Ps*.[26] In addition to cGMP, advanced therapies also need to comply with Good Tissue Practice (GTP) regulated under 21 CFR part 1271. Both GMP and GTP guarantee quality and safety. GTP has additional focus on the prevention or detection of infectious disease transmission.[11]

The FDA made an exemption for phase I clinical trials to fully comply with cGMP in 2008.[37] This is enabled for all investigational *drugs* in general under 21 CFR 210.2(c) and applies to some *biologic products* including advanced therapies.[35] Exemptions only apply to phase I trials, i.e. once the investigational drug advances to phase II, phase III, or on the market, the exemption is not applicable anymore (21 CFR 210.2(c)).

It is also recognized that the guidelines set out for phase I GMP requirements may not always apply to 351 GCT-based products. Sponsors are therefore encouraged to justify their manufacturing controls or other deviations from the guidelines in the submission dossiers.[35] The most important GMP aspects to take into consideration for advanced therapies during phase I include measures to prevent contamination and

cross-contamination, and to ensure product safety and quality, consistency in quality, and sterility.[11]

In order to determine by which specific manufacturing and quality standards combination products are regulated (*drugs*, *biologic products,* or *device*), specific guidance on how to comply with Current Good Manufacturing Practice Requirements for Combination Products is in development.[39]

Licensing / accreditation

Manufacturers of 351 GCT-based products need to comply with the BLA provisions. The BLA allows manufacturing by the applicant itself only, according to the manufacturing and testing methods and specifications on which the biologic license was granted (21 CFR 601.2). When there are multiple manufacturers involved in the development of a *biologic product*, each manufacturer needs to submit a BLA. Upon approval, they can be separately licensed for their part in the manufacturing process of a *biologic product*.[40]

When the BLA holder decides to outsource some or all of the manufacturing, the BLA holder needs to establish 1) a contract with the manufacturer; ensuring that the contract manufacturer is responsible for the safety, purity, and potency of the product, 2) compliance with the BLA provisions and 21 CFR 210, 211, 680, and 820, and 3) compliance with product and establishment standards. More details can be found in the guidance document: *Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics*.[40] These need to comply with sections 351 of the PHSA and section 704(a) of the FDCA, and they are subject to inspection by the FDA.

Batch release control

Quality control testing procedures are required before lots of advanced therapies can be sold and administered in the US. Suitable measures of sterility, contamination, purity, potency, identity and product characterization have been established upon BLA approval, including specifications of value limits that ensure that the lot is safe (21 CFR 610.11), potent (21 CFR 610.10), sterile (21 CFR 610.12), pure (21 CFR 610.13), and that identity (21 CFR 610.14) is confirmed. The exact testing methods will be product-specific, depending on its unique product characteristics. Specific guidance is provided for lot release testing for vectors.[41]

Release requirements for *biologic products* in general are regulated under 21 CFR 610 subpart A. All licensed biologic products need to be tested before release by the manufacturer (21 CFR 610.1), including advanced therapies products. For each lot the FDA may request to send samples and procedures for testing. Products are released under a Certificate of Analysis, which needs to include a summary of relevant product tests and results.[42] The FDA indicated that these Certificates of Analysis are product specific, but in general the same procedures are applicable for both autologous and allogeneic products. FDA regulations do not describe a role of 'Qualified Person'.

Contamination

Regulations for sterility tests, mycoplasma testing, and testing for adventitious viruses for *biologic products* can be found under 21 CFR 610. Sterility test method for *biologic products* are mandated and described under 21 CFR 610.12. It describes the requirements for culture-based methods and non-culture-based methods. However, it is possible that these methods are unsuitable for advanced therapies. For example, there could be insufficient volume available for both testing and treatment, or shelf-life may be too short to perform standard sterility testing. To overcome this issue of short shelf-life, alternative, additional methods may be used such as the rapid

microbial method. Alternative methods do need to be validated for reliability and consistency. If final product sterility cannot be determined in time before the shelf-life expires for use in clinical trials, sterility may need to be determined post-administration. In this case sponsors need to include action plans in their IND submissions. Sterility testing and testing for adventitious agents are as essential part of the CMC information that informed product safety.[15]

Guidance for microbiological contamination tests for advanced therapies is described in detail in the CMC guidance documents for *human somatic cell therapy* and *human gene therapy*.[13,14] If the standard culture-based assay to detect mycoplasma is not feasible, polymerase chain reaction (PCR)-based mycoplasma assays are recommended. Both in-vitro and in-vivo testing for viral contamination is recommended, plus specific guidance for various virus species is provided for advanced therapies. More detail on mycoplasma testing and testing for adventitious pathogens recommendations for advanced therapies can be found in the CMC guidance documents.[13,14] For gene therapy products extra testing for viral contamination may be required, because of the contamination risk with competent wild-type viruses or bacteria when using vectors in the product.[36]

Purity

Purity is defined as "relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product." Purity includes but is not limited to "relative freedom from residual moisture or other volatile substances and pyrogenic substances", under 21 CFR 600.3(r). Tests need to be performed to ensure that 351 GCT-based products are free from residual contaminants. Assays that can be used aim to detect unwanted cytokines, serum, or cell populations in the final product.[13,14]

Stability

Lack of long-term stability is often an issue for 351 GCT-based products. While still in development, stability of these product has to be assured and established through testing for the entire duration of the trial before subjects can be exposed to 351 GCT-based products (21 CFR 312.23(a)(7)(ii)). The stability test consists of a protocol of separate measures. A protocol of measures that needs to be included in an IND should include measures of sterility, identity, purity, quality, and potency, if these assays are available for investigational 351 GCT-based products. For each test, the method, the time points of measuring, temperature of measuring, and scientific rationale for using that test need to be included in the stability protocol. The tests need to cover the entire length of the proposed treatment duration as defined in the clinical protocol. It is recommended to perform stability testing at the start of processing, followed by in-process testing, and testing of the final product.[13,14]

At the time of filing a BLA, data to support a final formulation and expiration date needs to be included in the application. After marketing stability of 351 GCT-based products needs to be guaranteed also during distribution, in particular if it is delivered frozen.[13,14]

Potency

Control of potency is obligatory for all *biologic products*, including advanced therapies (21 CFR part 610).[37,43] Potency is an essential component of the CMC information that informs product quality.[15] Regulation under 21 CFR 610.10 mandates that "*Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner*

adequate to satisfy the interpretation of potency given by the definition in § 600.3(s) of this chapter."

Potency is defined as "*the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result*" under 21 CFR 600.3(s). Strength (which is equivalent to potency) is defined as "*potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data*" under 21 CFR 210.3(b)(16). This definition accounts for *biologic products*. For advanced therapies, potency may be supported by multiple laboratory tests that indicate various biologic properties, instead of one particular target binding that you would find for monoclonal antibodies for example.

Generally, potency control includes product characterization of biologic activity for example, and assays that indicate a potential mechanism of action. For advanced therapies, potential mechanisms of action are often dependent on multiple biologic mechanisms, or even poorly understood. Hence, the FDA is flexible in its approach in the evaluation of potency assays and takes a sliding-scale approach. Specific guidance on potency assays is available: *Guidance for Industry - Potency Tests for Cellular and Gene Therapy Products*.[43] Before the start of clinical trials, it is expected that assays have been developed with specifications that define acceptable value ranges. The evaluation of these assays and specifications becomes stricter throughout development. Before obtaining a license it is required that potency assays are validated. Several case studies of potency development strategies and assays have been described earlier.[44]

Traceability

Traceability requirements for 351 GCT-based products are the same as for HCT/Ps and regulated under 21 CFR 1271.290(b). A product tracking system needs to be established to ensure traceability of the starting material from the donor to the consignee or final disposition of the final product, and vice versa.[13,14]

For all biologic products, BLA holders need to submit distribution records to the CBER every six months. The frequency is subject to change if desired by the regulators. The bulk lot number, number of dosage units of each strength/potency plus lot numbers, label lot numbers, expiration dates on label, number of doses, and date of release need to be included in the records (21 CFR 600.81(a)).

3.4.6. Differences in manufacturing and quality requirements between autologous / non-autologous products

There are differences in donor eligibility and screening procedures between autologous and non-autologous products. For autologous products donor eligibility and screening procedures are recommended, but for non-autologous products this is mandatory (see section 3.4.1).

Other manufacturing standards for advanced therapies are the same between autologous and non-autologous products, including lot testing requirements. As discussed throughout this section, protocols for quality control may differ based on the unique product characteristics (e.g. it mechanisms of action, use of vectors, small volume) of the product.

3.4.7. Description of processes of approval of changes in manufacturing processes of advanced therapies

When changes occur in the manufacturing process after approval, a risk-based approach is in place to determine whether additional studies or requirements are necessary for approved biologic products.[42] Changes in the manufacturing process are categorized and reported to the FDA by the manufacturer as 1) major change, 2) moderate change, and 3) minor change:[45]

Major changes are defined as a change "*that has a substantial potential to have an adverse effect on the safety or effectiveness of the product*." Consequently, a Prior Approval Supplement needs to be submitted to the FDA. Before distribution of the changed product, approval is required (21 CFR 601.12(b)).

Moderate changes are defined as a change "*that has a moderate potential to have an adverse effect on the safety or effectiveness of the product*." Consequently, a Changes Being Effected in 30 days Supplement needs to be submitted to the FDA at least 30 days before distribution of the changed product. The FDA needs to approve the changes provided in the supplement, and it may decide to cease distribution of the changed product (21 CFR 601.12(c)).

Minor changes are defined as a change "*that has a minimal potential to have an adverse effect on the safety or effectiveness of the product."* The changes to the product need to be described in the Annual Report. There are no further consequences for minor changes. Products can be classified into a lower risk group if potential risks of adverse effects are reduced (21 CFR 601.12(d)).

3.5. Post-marketing requirements for advanced therapies

3.5.1. Post-marketing requirements of advanced therapies vs. chemical-based medicines

FDA does not have standards for post-marketing requirements that specifically apply to advanced therapies. For all *drugs* and *biologic*, clinical and non-clinical studies may need to be conducted in order to provide additional data on safety, efficacy or clinical use. These studies are described in the guidance document: *Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug and Cosmetic Act (July 2009).*[46] We will discuss general post-marketing requirements in this section and describe post-marketing requirements that have been imposed upon advanced therapies in the next section (section 3.5.2).

There are two categories of post-marketing studies in the US: (1) Post-Marketing Requirements (PMRs) that are mandatory to conduct and a condition for approval under the Food and Drug Administration Amendments Act of 2007 (FDAAA), section 505(o); (2) post-marketing commitments (PMCs) to which a sponsor commits, but which are not legally-binding.[47] Under section 506B of the FDAAA annual reports are required for both PMR and PMC[48] under 21 CFR 314.81(b)(2) for drugs, and under 21 CFR 601.70 for biologic products.

Depending on the data included in the BLA submission, it may be required to conduct PMRs to investigate a known serious risk of the drug, signals of serious risks of the drug, and detect any unexpected serious risks of the drug. The FDA is authorized to obligate such studies since the enactment of the Food and Drug Administration Amendments Act of 2007 (FDAAA), section 505(o).[47] Other situations that require the conduct of PMRs are to support clinical benefit for chemical-based drugs (21 CFR 314.510) or biologic products (21 CFR 601.41) that were approved under an

accelerated approval pathway (see section 3.3.2), or those approved on preclinical data under the Animal Efficacy Rule (21 CFR 314.610(b)(1); 21 CFR 601.91(b)(1)), plus post-marketing paediatric studies that are required under the Paediatric Research Equity Act for drugs (21 CFR 314.55(b)), or biologic products (21 CFR 601.27(b)).[47]

The available guidance document indicates specific types of studies that may be required to improve understanding of a known serious risk of the drug, signals of serious risks of the drug, or to detect any unexpected serious risks of the drug.[46] Based on the information of these studies FDA may mandate labelling change, require manufacturing changes or withdraw the product from the market in case of serious safety concerns.

3.5.2. Description of post-marketing requirements specific for advanced therapies

There is no specification of the regulation with regard to Post Marketing Commitments or Post Marketing Requirements of advanced therapies. Therefore, we provide an overview of all PMRs and PMCs for each of the ten approved advanced therapies in Table 3.4. Specific information was found in databases that list post-marketing requirements and commitments for drugs (including biologic products),[47] plus Summary Basis for Regulatory Action documents.[49]

Follow up periods for patients that received *gene therapy products* may need to extend for longer periods to capture delayed adverse events. These events may occur much later than for other products, because of prolonged expression of transgenes or altered expression of endogenous genes. This could lead to malignant formation or other adverse events. To provide guidance, the FDA has published a guidance document how to take possible delayed adverse effects into account in the design of preclinical studies, clinical studies, and long-term follow up for patients that received specific types of gene therapy products: *Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events*.[21] A minimum of 15 years for follow-up observations are recommended by the FDA if there is a risk of delayed adverse effects. A developer of a human gene therapy confirmed this approach of the FDA. However, the recommendation of 15 years follow up can be influenced by product specific properties, such as duration of in-vivo vector persistence and duration of in-vivo transgene expression.[21]

3.6. Routes for patients to have access to advanced therapies outside of clinical trials and marketing authorisation

Investigational products, including advanced therapies can be made available to patients outside a clinical trial via the expanded access pathway. The goal of this pathway is to make promising products available to patients for treatment rather than research purposes. Expanded access is regulated under 21 CFR 312 subpart I, and is available for three patient categories: individual patients (21 CFR 312.310), intermediate-size patient populations (21 CFR 312.315), and for wide use under a protocol (21 CFR 312.320).[5] Criteria that must be met to authorize the use of expanded access are specified in 21 CFR 312 and further discussed in the guidance document *Guidance for Industry: Expanded Access to investigational Drugs for Treatment Use – Qs& As.*[50] In short, the following criteria apply:

> "1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use." (21 CFR 312.305).

Applicants need to submit a document containing information on rational for intended use, patient eligibility, a description of the manufacturing facility, route of administration, toxicology data, and approval of an IRB.[51] If the FDA receives many requests for expanded access for individual treatment that are for the same use, request may be consolidated under 21 CFR 312.315. Widespread treatment use may be permitted if the regulations under 21 CFR 312.320 are adhered to; widespread expanded access can be granted when clinical trials for marketing authorisation are on-going, have ended, marketing approval is being pursued, or there is enough supporting evidence for safety and efficacy to grant expanded access. There are no other means than mentioned in this section by which patients can have expanded access to advanced therapies.

3.7. Views of stakeholders on the regulatory framework

Advanced therapies are regulated within the general framework for medicinal products in the US. Within this framework, advanced therapies are regulated as *biologic products,* which are legally defined and for which general guidance documents is available (351 GCT-based products). In addition, the FDA has published various guidance documents that are specific for advanced therapies mentioned in Figure 3.3.

3.7.1. Factors facilitating development and availability of advanced therapies in the US

General:

- US developers and association were positive on the interaction and collaboration with the FDA. Engaging with the FDA during development was highlighted as essential, because of the scientific challenges that are encountered during the development of advanced therapies (see section 3.7.2);
- Some US developers were satisfied about the inclusion of advanced therapies in the same approval process as all other *biologic products*. An association did indicate that FDA is aware of the challenges that this brings and that they are involved in initiatives to develop better, more specific manufacturing and quality standards for advanced therapies;
- US developers felt that the OCTGT is very capable to work with complex and varying product characteristics of advanced therapies. They felt that assessors were familiar with the scientific challenges that are associated with advanced therapies. However, other centres within the FDA that are responsible for therapeutic areas were described as less flexible in their approach to advanced therapies;
- US developers and association indicated that due to the large market, volume of research institutions and large venture capital, and a less risk-averse attitude compared to other jurisdictions, US takes a world-leading position in R&D activities.

Manufacturing and quality:

- As development of advanced therapies progresses, manufacturing and quality standards that need to be adhered to become more stringent. One US developer referred to this as a so-called *sliding-scale policy*. The policy ensures that manufacturing and quality standards are guaranteed upon marketing authorisation, but at the same time enables flexibility in manufacturing and quality standards in earlier phases of development. This can be crucial for viable development of advanced therapies that are still in early development, given that it is not always possible to generate sufficient data for demonstrating safety and quality.

Adaptive approval procedures:

- There are several regulatory pathways in place within the US regulatory framework that facilitate development or expedite approval such as breakthrough designation regulatory pathways. These were perceived as facilitative for the development of advanced therapies. In fact, some of the approved advanced therapies in the US have used these pathways.

3.7.2. Factors hampering development and availability of advanced therapies in the US

In general, US developers and association perceived the regulatory process as challenging given the absence of general standards for clinical trial design and manufacturing and quality. This was perceived to be particularly the case when advanced therapies were developed for rare indications for which no precedents had been established. If there is not standard or comparable treatment available, developers have to engage in partnerships with physicians to develop appropriate outcome measures.

General:

- Although US developers were knowledgeable about the requirements that are in place for advanced therapies, they sometimes felt that specific standards for their advanced products, especially for CMC and clinical trial design, were missing (see below for details);
- Even in the US, it seems to be difficult to secure funding for early stage clinical trials.

Specific hampering factors that were mentioned were:

Manufacturing and quality:

- Due to the often novel and unique product characteristics of advanced therapies, the specific standards for manufacturing and quality testing methods typically co-develop as product development progresses to more advanced stages. An association highlighted the lack of clarity about manufacturing and quality standards in some domains as a key barrier for development of advanced therapies. Lack of clarity may result in inefficient product development because the FDA and developers need to evaluate and develop certain manufacturing and quality standards along the development process for each advanced therapy separately. Moreover it can also result in feedback loops where - in the attempt to develop safe and quality advanced therapies - requirements and protocols for manufacturing and quality standards keep changing with progression of knowledge about product characteristics;

- The lack of specific manufacturing and quality standards for advanced therapies was described as an issue by a developer due to problems with consistency of the product and the lack or unsuitability of assays;
- It was mentioned that the donor eligibility regulations are challenging for research on embryonic stem cells. The regulations mandate that all medical history needs to be collected and that donors are anonymous. The design for these regulations originates from research and development with somatic starting material, not embryonic starting material;
- Quality testing for adventitious agents can be very challenging for advanced therapies. The specific tests to be used depend on the product characteristics and no clear guidance is available.

Clinical trials:

- The design of early-stage clinical trials can pose challenges for developers. Advanced therapies have their own specific set of safety concerns such as tumourigenicity and proliferation in untargeted tissues. Considering these safety concerns, the administration route is of key importance as it will influence how these products distribute to targeted tissues, but also untargeted tissues for example. It was indicated that safety in general, a safe initial dose and a theoretical reason for efficacy are focus points of the FDA during early-stage clinical trials;
- Potentially invasive delivery methods can prevent placebo-controlled clinical study designs. Small patient populations impose statistical difficulties for clinical study designs. In addition, advanced therapies often target diseases or conditions for which there is no comparable treatment available. Consequently, outcome measures are unavailable. Developers indicated to partner with physicians to develop better clinical outcome measures for such diseases or conditions. A US developer indicated that for those therapeutic areas for which clinical endpoints that serve as primary outcome measures are in place, these may not be suitable to indicate efficacy for cell-based therapies.

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4. Analysis of the regulatory framework governing advanced therapies in Canada

4.1. Overview of regulatory framework for advanced therapies in Canada

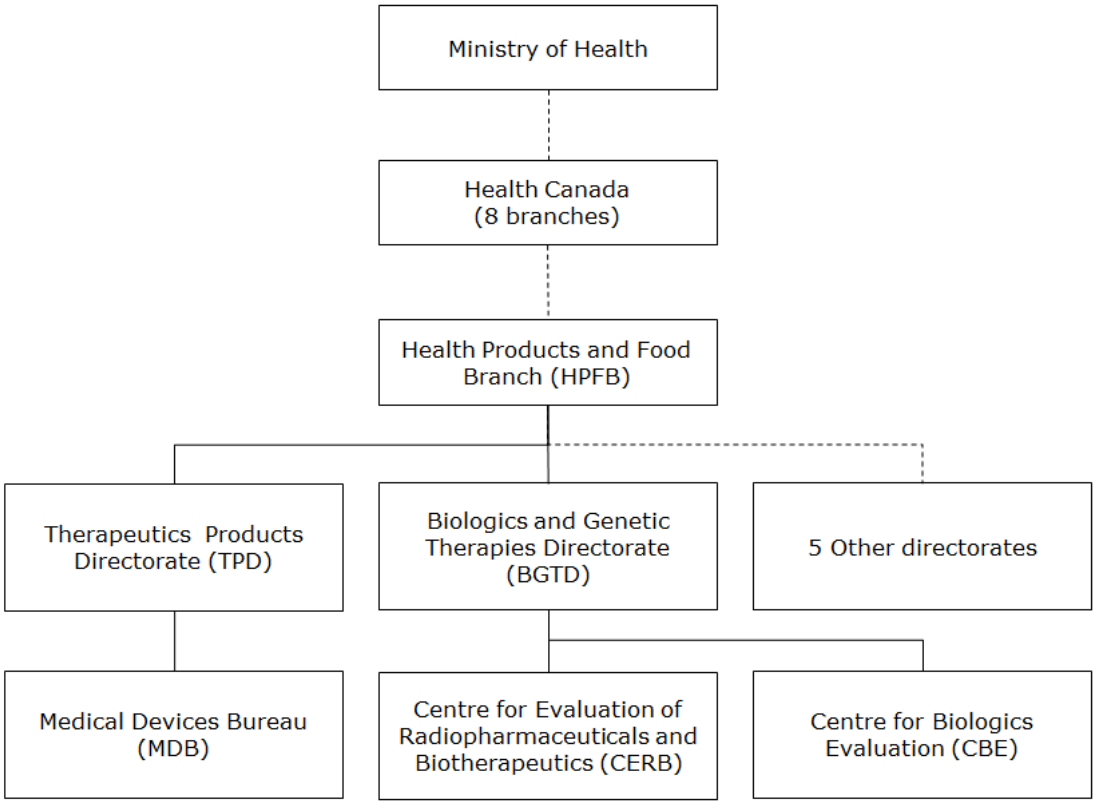
4.1.1. Regulatory responsibilities and mandate

Health Canada regulates the distribution of health products in Canada. Regulatory responsibilities cover drugs and other medicinal products. They include assessment and approval of clinical trial applications (section 4.2); marketing approvals of medicinal product based on assessment of quality, safety and efficacy of a product (section 4.3) and oversight of post-marketing activities (section 4.5). There are other provincial regulatory authorities that are responsible for health administration and medical practice.

Within the agency responsibilities for drugs and medical devices are spread across different directorates and bureaus located within the Health Products and Food Branch. The Therapeutics Products Directorate (TPD) is the directorate for chemical-based drugs and medical devices. The Biologics and Genetic Therapies Directorate (BGTD) is the department that evaluates applications of *biologic drugs*.[1]

Regulation of advanced therapies is primarily the responsibility of two Centres within BGTD. The Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB) shares product responsibilities for cell therapy products with the Centre for Biologics Evaluation (CBE), while CERB is responsible for gene therapy products. (see Figure 4.1).[2] Furthermore, combination products may fall under the responsibility of the Medical Devices Bureau (MDB) of the TPD (section 4.3.3).

Figure 4.1 Directorates of Health Canada involved in the regulation of GCT-based product



4.1.2. Regulatory framework for advanced therapies

The Canadian regulatory framework for evaluating advanced therapies is enacted on three different levels consisting of acts, regulations, and guidance for developers. Acts provide scope, high-level principles and the legal authority to make Regulations; Regulations interpret the Acts and provide general details on implementation activities; Guidelines interpret the Regulations and provide non-legally binding guidance on development and assessment activities.[2]

In Canada, advanced therapies as defined in this report are regulated as a *drug* under the Food and Drugs Act.[3] The applicable Regulation under the Food and Drugs Act are the Food and Drugs Regulations (FDR) Part C.[4] Combination products may be classified as *device* (see section 4.3.3) and regulated under the Medical Devices Regulations (MDR).[5] Within drugs, Health Canada distinguished *biologic drugs* as a subclass (Schedule D). The specific regulations for these *biologic drugs* are similar to other (chemical-based) *drugs* regulated under Part C of the FDR, except for product quality standards that are specified in Division 4 of the FDR (see section 4.4).

Gene therapy products are always regulated as *biologic drugs* under part C of the FDR as they are listed as a specific class of drugs on Schedule D of the Food and Drugs Act: "*drugs obtained by recombinant DNA procedures*".[3] Other drugs listed on Schedule D include *biologic drugs* such as monoclonal antibodies, cytokines, hormones and drugs made of blood.[6] In guideline documents, advanced therapies are loosely referred to as gene therapy products and cell therapy products. However, cell therapy products are not listed as a specific class of drugs on Schedule D or any other Schedule in the Food and Drugs Act. Product definitions are provided in Table 4.1.

Table 4.1 Product definitions

Product type	Definition
Drug (Food and Drug Act, Section 2)	Includes any substance or mixture of substances manufactured, sold or represented for use in: a. the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals; b. restoring, correcting or modifying organic functions in human beings or animals; or c. disinfection in premises in which food is manufactured, prepared or kept.
Biologic drug (Food and Drug Act, Section 12)	All products listed on Schedule D: ▪ Allergenic substances used for the treatment or diagnosis of allergic or immunological diseases; ▪ Anterior pituitary extracts; ▪ Aprotinin; ▪ Cholecystokinin; ▪ Drugs obtained by recombinant DNA procedures; ▪ Drugs, other than antibiotics, prepared from micro-organisms; ▪ Drugs that are or are made from blood; ▪ Glucagon; ▪ Gonadotrophins; ▪ Immunizing agents; ▪ Insulin; ▪ Interferon; ▪ Monoclonal antibodies, their conjugates and derivatives; ▪ Secretin; ▪ Snake Venom; ▪ Urokinase.
Device (Food and Drug Act, Section 2)	An instrument, apparatus, contrivance or other similar article, or an in vitro reagent, including a component, part or accessory of any of them, that is manufactured, sold or represented for use in: a. diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physical state, or any of their symptoms, in human beings or animals; b. restoring, modifying or correcting the body structure of human beings or animals or the functioning of any part of the bodies of human beings or animals; c. diagnosing pregnancy in human beings or animals; d. caring for human beings or animals during pregnancy or at or after the birth of the offspring, including caring for the offspring; or e. preventing conception in human beings or animals.
CTO therapy (CTOR, Section 2)	Organs and minimally manipulated cells and tissues.

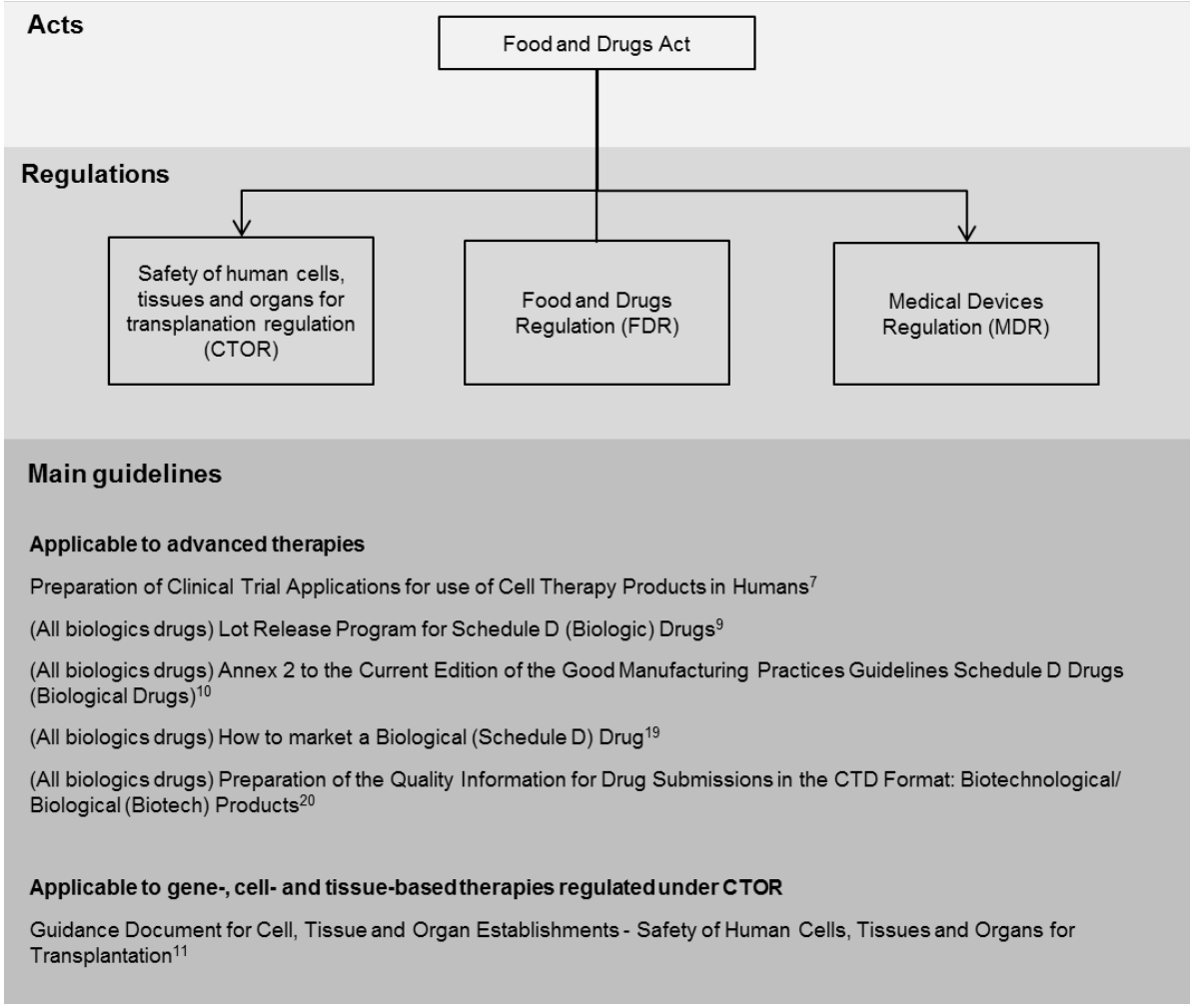
Cell therapy products are considered a *drug* and regulated under the FDR, except if they meet the inclusion criteria under the Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTOR; see section 4.1.3). This implies that cell therapy products that are regulated as a *drug* are more-than-minimally manipulated, or xenogeneic, or for non-homologous use, or have a systemic effect or depend on their metabolic activity for their primary function.[2] Relevant definitions are provided in section 4.1.3.

Health Canada recently developed a specific guidance document for cell therapy products that fall under the FDR. This guideline provides assistance as to how to prepare Clinical Trial Applications (CTA - section 4.2) for cell therapy products: *Guidance documents: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans*.[7] It covers three issues: chemistry, manufacturing and control (CMC), preclinical studies and early versus late stage clinical trials.[8] There are no guidance documents for other types of advanced therapies, such as gene therapy products.

There are also general guidelines applicable to all *biologic drugs* listed on Schedule D that are of relevance for the regulation of advanced therapies, including: *Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs*;[9] and *Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs)*.[10]

Health Canada adopts all International Conference on Harmonisation (ICH) guidelines and in the absence of specific Canadian or ICH guidance, Health Canada may refer to guidance developed by the US Food and Drug Administration and the European Medicines Agency.[2] Health Canada also indicated to be in consultations with interested and affected stakeholders on how to improve requirements related to Good Manufacturing Practice (GMP) for cell therapy products (section 4.4). An overview of all relevant regulations and guidance documents that are applicable for the regulation of advanced therapies is provided in Figure 4.2.

Figure 4.2 Overview of regulations and guidance documents relevant for GCT-based therapies



4.1.3. Products exempted from the requirements to obtain marketing authorisation

Cells, tissues and organs that are intended for transplantation are regulated under the CTOR when they are allogeneic, minimally manipulated, and for homologous use (Figure 4.3).[11] Health Canada indicated that they do not consider therapies under the CTOR as advanced, neither do these therapies adhere to the definition of advanced therapy in this report. It is likely that cell therapies will have a systemic or metabolic effect, which effectively declassifies them from the CTOR.[8] Definitions of the criteria for falling under the CTOR are as follows:[11]

"*allogeneic use*", defined as "*transplantation from one individual to another*".[7]

"*homologous", "in respect of a cell, tissue or organ, means that the cell, tissue or organ performs the same basic function after transplantation*" (CTOR, Section 1).

"*minimally manipulated" means:*

a) *"in respect of a structural tissue, that the processing does not alter the original characteristics that are relevant to its claimed utility for reconstruction, repair or replacement; and*

b) *in respect of cells and non-structural tissue, that the processing does not alter the biological characteristics that are relevant to their claimed utility*" (CTOR, Section 1).

If cells have a systemic effect or if they depend on their own metabolic activity for their function they are regulated under the FDR, except for islet cells and lymphohematopoietic cells that are derived from bone marrow, peripheral blood or cord blood (CTOR, Section 3).[12] These cells are regulated under the CTOR irrespective of their metabolic effect. [11] If any of the materials that are regulated under the CTOR become subject to clinical trial testing, they will be regulated under the FDR as *drugs* (CTOR, Section 4.3). Furthermore, if cells have all characteristics of cells under the CTOR but are of autologous instead of allogeneic origin they may be regulated under the FDR and not under the CTOR.[8] Health Canada confirmed that the FDR may be applicable for these autologous cells, but this is determined on a case-by-cases basis. It may also be that these therapies are prepared and administered under unique circumstances ('at the bedside') and fall outside of Health Canada's ability to regulate.

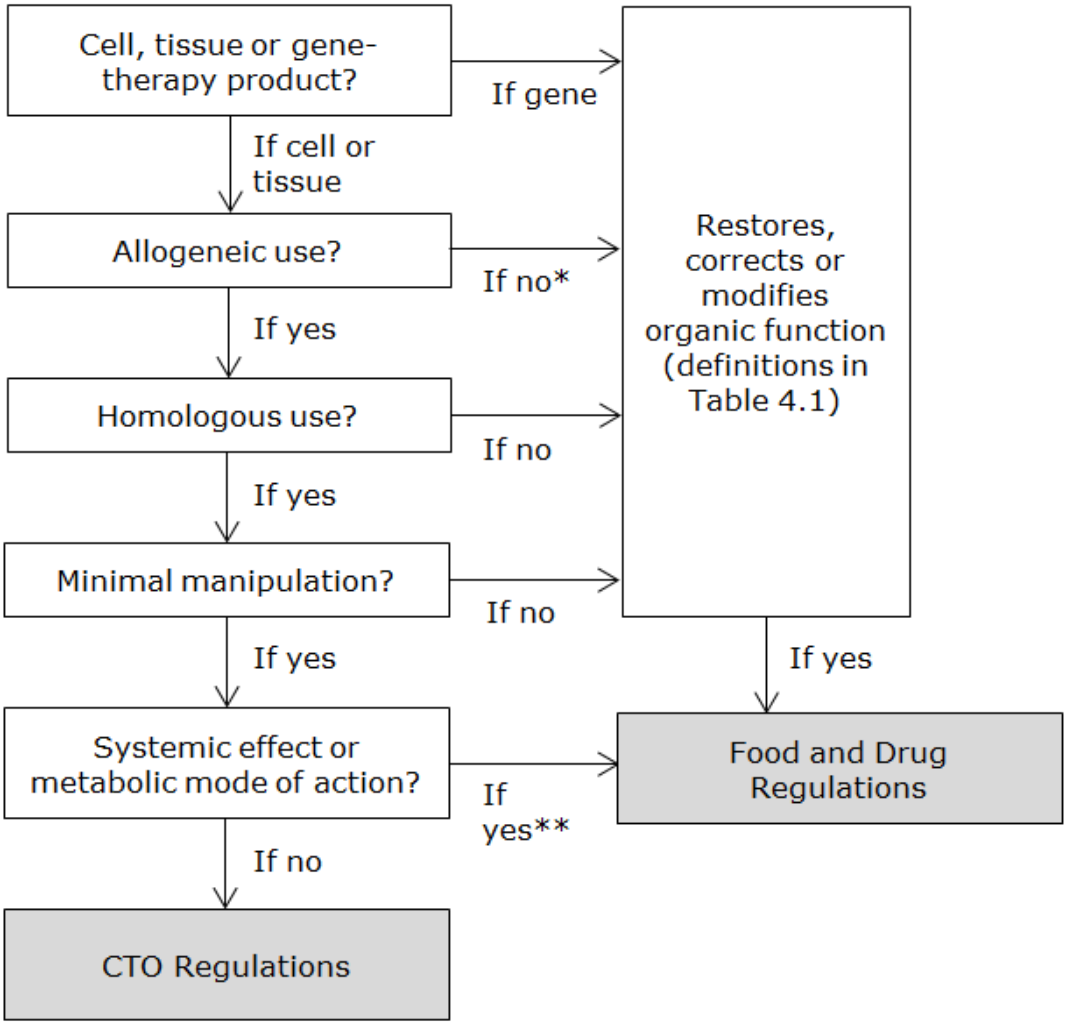
"*systemic effect*" is defined as "*a consequence or effect that is either of a generalized nature or that occurs at a site distant or not related to the location of the cell or tissue*" (CTOR, Section 3).

"*metabolic effect*" refers to a mode of action that relate to the production of hormones or cytokines for example.

Health Canada indicated that the distribution of gene-, cell- and tissue-based products are not regulated under any other Acts or regulations than the Food and Drugs Act, FDR, MDR, or CTOR.

The creation of embryonic stem cells for research purposes is prohibited under the Assisted Human Reproduction Act of Canada. Embryos that are no longer needed for in vitro fertilization procedures can be used for research purposes, if permitted by the parents after full informed consent.[8]

Figure 4.3 Decision-tree to classify products as drugs under the Food and Drug Regulations, or as cells, tissues or organs for transplantation



* It may be decided on a case-by-case basis that autologous products are not regulated by Health Canada under 'by the bedsite' circumstances. ** Except islest cells and lymphohematopoietic cells derived from bone marrow, peripheral blood or cord blood. Figure adapted from Viswanathan and Bubela (2015)[8]

4.1.4. Description of methods to control advanced therapies without therapeutic indication

Health Canada indicated that all cell-based cosmetic products are regulated either under the FDR, MDR, or CTOR. If these adhere to the definition of *drug* or *device*, marketing authorisation is mandatory. In general, it is unlikely that advanced therapies without therapeutic indication are administered to patients in Canada.

4.2. Framework governing clinical trials with advanced therapies

Since advanced therapies are regulated in Canada as *biologic drugs* under the FDR, we will discuss the procedures for clinical trial applications for *biologic drugs* in the next

section. Moreover, we will discuss main differences between clinical trial applications for advanced therapies and chemical-based drugs (section 4.2.2).

4.2.1. Responsible parties and tasks for clinical trial authorisation and supervision

Clinical trial authorisation of advanced therapies regulated as drugs

Authorisation for clinical trials is the responsibility of the BGTD of Health Canada. Authorisation is required for advanced therapies that are listed on Schedule D of the Food and Drugs Act (commonly referred to as *biologic drugs*). It is also required for cell and tissue therapies under the CTOR that become subject to testing in clinical trials.

To gain authorisation for a clinical trial, the sponsor needs to submit a Clinical Trial Application (CTA) to Health Canada, as specified under Division 5 of the FDR. As part of the CTA, the manufacturer is obligated to submit all relevant product and manufacturing information that is needed to gain approval to use new investigational drugs in the conduct of clinical trials with the drug (FDR, Section C.08.005).

There are general CTA requirements that account for all Schedule D *biologic drugs*, including advanced therapies. These general requirements act as a rough guidance for advanced therapies. The outline of a CTA follows the ICH Common Technical Document (CTD).[13] The CTA is a living dossier that needs to be updated when new relevant information is available and new clinical trials are initiated. Critical information for *biologic drugs* CTAs includes:

- chemical and manufacturing information and accompanying safety and efficacy data originating from non-clinical and clinical data;
- lot release information (see section 4.4);
- a listing of all production sites;[14]
- all data from preclinical studies should adhere to GLP.[15]

In addition to these general requirements for *biologic drug* CTAs, Health Canada recently published a guidance document on how to prepare CTAs for cell therapy products specifically: *Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans*.[7] A CTA for cell therapy products needs to include results from preclinical studies to indicate potential risks and the administration route of the cell therapy. There are a number of essential preclinical studies that are requested by the BGDT that can identify potential risks of the treatment. These include, but are not limited to, studies on tumourigenicity, biodistribution and engraftment studies, ectopic tissue forming potential, identification of a safe and tolerable dose, immunogenicity, and other studies that relate to the specific product characteristics of the cell therapy product.

Preclinical studies should comply with Good Laboratory Practices (GLP), but for some studies an exception may be made on a case-by-case basis. For those studies that are not GLP compliant, data quality needs to be guaranteed with scientific rationales.

CTA requirements that were mentioned as most important by developers of cell therapy products included evidence for a mechanism of action and safety concerns, such as migration of cells to untargeted tissues and tumourigenicity. Other important aspects include the route of administration and margin for clinical dose in a clinical

trial protocol. It was also mentioned that in regulatory practice, it should be clear how much of the clinical trial protocol is based on data from pre-clinical studies in a CTA.

BGTD authorizes clinical trials for *biologic drugs* by issuing a No Objection Letter within 30 days.[16] Authorisation of cell therapy products is based on an assessment of preclinical, quality aspects, and possible clinical data (if available) by a review team. In order to gain early clinical trial authorisation, the risk-benefit profile needs to be acceptable, clinical trials needs to be in the interests of the participants, and objectives of clinical trials need to be achievable. Health Canada recommends to generate efficacy data, however, it acknowledges that generating efficacy data from animal studies may not be possible with cell therapy products.[7] After clinical trials are authorized, any relevant updates about testing need to be send to Health Canada. This includes notifications related to the manufacturing process, protocol amendments, discontinuation, resumption and completion of a trial, and safety reporting.[14]

Sponsors also need to obtain approval of the study protocol and informed consent forms by the Ethical Review Board (ERB) of each clinical trial site that is involved in the study, prior to filing a CTA at Health Canada (FDR, Section C.05.006(1)(c)). For each ERB a signed statement of compliance with good clinical practices (GCP) needs to be included in the CTA. The sponsor needs to ensure that research is conducted according to ICH-GCP[17] at each site, including safety reporting to the ERB by the Qualified (Primary) Investigator.[14]

For changes in product processing, procedures that are applicable to *biologic drugs* are applied to cell therapy products.[7] CTA amendments or notifications need to be submitted to Health Canada, particularly when product quality or safety is affected. If the processing change is substantial, a new CTA submission may be required. [14] However, it may be that for CTAs for cell therapy products not all quality and manufacturing data is required, as some information may not yet be available depending on the development phase.[13,14] For example, potency assays to indicate in-vivo mechanisms of action may not yet be available when filing a CTA.

Health Canada confirmed that cell therapy products are subject to testing for consistency of a few lots by the sponsor as part of the Lot Release Programme for *biologic drugs* during clinical development. Therefore, the sponsor is required to sign a certificate stating that lots were tested according to product specifications that are developed throughout preclinical and clinical studies.[14] Details of the lot release for *biologic drugs* are described in more detail in section 4.4.

4.3. Framework governing commercialisation of advanced therapies

4.3.1. Procedures for advanced therapies vs. chemical-based medicines

In general, the sections of the FDR that are applicable to the authorisation of *biologic drugs* are Division 1 (Labelling, Drug Identification Numbers); Division 1A (Establishment Licenses); Division 2 (Good Manufacturing Practices), Division 4 (Biologics); and Division 8 (New Drug Submissions).[4] Division 5 (Clinical Trial Applications) has been discussed in section 4.2. Division 4 (Biologics) is the division that is specific to *biologic drugs* including advanced therapies. It mandates specific manufacturing standards for marketing approval (section 4.4.1).

Marketing approval for a product in Canada requires the filing of a New Drug Submission (NDS) at Health Canada as mentioned in Division 8 of the FDR. The NDS document has been standardized according to the CTD template of the ICH.[18] A CTD

typically includes information on the organisation, quality (chemistry, manufacturing, controls), plus safety and efficacy data from preclinical and clinical studies (phase I-III).[13] There is guidance as to how to use the CTD format while preparing submissions in general.[13] However, there are no specific guidance documents how to use the CTD format for *biologic drugs* or for advanced therapies specifically. Health Canada does provide regulatory guidance for *biologic drugs* on how to comply with regulations for clinical trials, premarket submissions, facility information, product labelling, Good Manufacturing Practices (GMP), establishment licensing, and lot release.[19]

To prepare for a CTD, Health Canada requires Certified Product Information Document forms that are specific to biologics, radiopharmaceuticals, and chemical-based drugs.[20] These documents should contain summaries of quality information. Complete quality and manufacturing information is required while submitting a NDS.[19] Compared to chemical-based drugs, Health Canada requires more detailed information on chemistry and manufacturing of *biologic drugs* to ensure purity and quality of the product (see section 4.4.1).[21]

In order for a *biologic drug* to be approved by the BGTD sufficient scientific evidence must be provided which shows that the drug is safe, efficacious, and of suitable quality.[21] Health Canada assesses the benefit-risk profile of the drug on a case-by-case basis. When evidence supports safety, efficacy and quality, a Notice of Compliance (NOC) is issued and the drug is assigned a Drug Identification Number (DIN). A Notice of Deficiency (NOD) is issued when there is not enough information to make a risk-benefit decision. A Notice of Non-Compliance (NON) is issued when the benefits of the product do not outweigh the risk.[8] When the primary full submission has been accepted, the standard regulatory review process can take up to 300 days.[16]

Advanced therapies need to adhere to similar standards for safety, efficacy as other *biologic drugs* listed on Schedule D. Health Canada did recently publish a guideline how to prepare CTAs for cell therapy products, including guidance for quality aspects, pre-clinical, and clinical studies.[7] However, there are no guidelines in place for marketing authorisation for advanced therapies, or specific guidelines for gene therapy products. Concerning safety, Health Canada refers sponsors to other guidance documents for vector safety; the ICH guidance document for safety testing of vectors,[22] ICH standards to address vector shedding,[23] ICH standards to address inadvertent germline integration of gene therapy vectors,[24] and ICH guidelines for oncolytic viruses.[25] Sponsors may also use the US Food and Drug Administration guidance document for cell and gene therapy[26] and the European Medicines Agency paper on risk management of insertional mutagenesis following gene therapy.[27] This additional information should provide sufficient data to counterproof possibilities of administering viruses that can replicate and spread from the genes to other tissues or patients.[8]

4.3.2. Schemes to facilitate early approval

In addition to a full marketing authorisation based on comprehensive data, advanced therapies can be registered under a Notice of Compliance with conditions (NOC/c). This policy allows accelerated market authorisation when a sponsor demonstrates that the new product has the potential to improve the benefit-risk profile compared to standard treatment. NOC/c can only be used for products that treat serious, life-threatening or severely debilitating diseases or conditions, for which current treatment has a poorer safety and efficacy profile, or no treatment is available.[28]

Data that can be used for NOC/c include the use of validated surrogate markers as endpoints, phase II trials that require validation through phase III trials, or phase III trials with a small sample size that require either efficacy or safety confirmation. The

NOC/c policy requires completion of confirmatory trials in the post-marketing phase to support the claimed clinical benefit and for enhanced post-market surveillance (section 4.5). Products marketed under the NOC/c policy also need to adhere to enhanced labelling requirements.[28]

For life-threatening or severely debilitating diseases or conditions, it is also possible to obtain a priority review for a NDS. To apply for a priority review, there has to be substantial evidence of clinical effectiveness for 1) diseases or conditions for which there is no treatment available, or 2) to indicate a significant improvement of the risk-benefit profile over currently available treatment.[29] The time frame under the Priority Review Policy for screening is shortened from 45 to 25 days, for review of full submissions it is shortened from maximum 300 to 180 days.[16]

4.3.3. Regulation of incorporated medical devices

Products that are a combination of a biologic and a medical device product are regulated as combination products either under the FDR or MDR, depending on which component is related to the principal mechanism of action, or the claimed effect or purpose.[2] Health Canada also indicated that regulation of a combination product under the FDR and MDR is possible, if a combination product consists of separate components that are distributed separately.

If a product is regulated under the MDR, developers need to apply for a medical device license. Licenses are granted by the MDB, which is a department of the TPD.[30] However, if there are no sales or advertisement for a medical device it is exempted from the MDR and its license requirement (see section 4.7). Manufacturers of medical devices need to comply with International Organization for Standardization (ISO) 13485.[8]

4.3.4. Possibility to rely on data other than clinical trials for demonstration of efficacy and safety

At the time of writing, no specific regulations or guidelines were in place for the approval of advanced therapies. Sponsors need to follow the regulations and guidelines for *biological drugs* as a rough guidance. For *biologic drugs*, data from clinical trials is necessary to obtain marketing authorisation. Health Canada confirmed that it is necessary to submit evidence of efficacy in order to gain marketing authorisation under standardized approval procedures (see section 4.3.1). This rule also accounts when sponsors apply for a Notice of Compliance with conditions. In this case, initial clinical efficacy data that is promising has to be provided. Authorisation of Special Access (see section 4.6) cannot replace the conduct of pivotal trials for marketing authorisation of *drugs*, including advanced therapies.[31]

Health Canada indicated that there is only one possibility to apply for market authorisation without clinical data. In case of emergency situations as specified in section C.08.002.01 of the FDR, sponsors may apply for Extraordinary Use New Drug Submission without clinical efficacy evidence.

4.4. Manufacturing and quality requirements for advanced therapies

There are no specific quality and manufacturing regulations in place for advanced therapies in Canada. In general, all manufacturing and quality regulations including Good Manufacturing Practice (GMP) for *biologic drugs* also apply to advanced therapies. Health Canada indicated that not all requirements for *biologic drugs* can be directly translated to the specific characteristics of advanced therapies. Health Canada also indicated to be involved in discussions with interested parties on GMP

requirements that are specific for cell therapy products. However, at the time of writing, all drugs including *biologic drugs* and cell therapy products need to comply with the same GMP regulations under Division 2 of the FDR.

There are two guidance documents that can be used for the interpretation of the GMP regulations for advanced therapies. First, a guidance document that is specific to GMP for *biologic drugs* is available: *Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs)*.[10] Second, in order to be able to interpret the general GMP regulations for cell therapy products, some key specificities of manufacturing and quality standards for advanced therapies (compared to *biologic drugs*) are included in the recently published guideline document on CTAs for cell therapy products.[7] However, specific guidance on which protocols to use for manufacturing and quality is not provided. Hence, protocols for manufacturing procedures and quality testing for advanced therapies are determined during development on a case-by-case basis and develop over the development life-cycle as preclinical and clinical studies progress.

As development progresses, regulatory standards for manufacturing and quality tend to become more stringent. Whereas manufacturing protocols and quality procedures do not have to be fully standardized during early development, manufacturing protocols and quality procedures need to be standardized and consistent upon marketing approval.

The manufacturing and quality standards for *biologic drugs* for approval are more rigorous than for *drugs*. Methods of manufacturing must be provided in more detail as part of an NDS, on-site inspections of manufacturing sites prior to approval are required, and quality of *biologic drugs* is tested for each lot in the post-marketing phase.[21] Below we discuss manufacturing and quality requirements for *biologic drugs* and specify them for cell therapy products where possible.

4.4.1. Starting materials

For starting materials of human or animal origin, the infectious disease donor screening and testing requirements that originate from the CTOR can be used as a reference for advanced therapies that are regulated under the FDR. Any deviations from these standards need to be justified. Health Canada also refers to the CTD Modules 3.2.S.2.2 and 3.2.S.2.3 for more guidance. In short, donor screening refers to a medical, social history, and physical examination.[7] Donors are also tested for infectious diseases.[8] When cells are obtained from a third party, information needs to be provided to indicate that all measures were taken to detect infectious diseases in donor material. If screening, testing, and record keeping is not up to Canadian standards, additional screening or testing may be required. For material of animal origin it is important that the risk for Transmissible Spongiform Encephalopathies (TSE) transmission is taken into consideration.[7]

More broadly, raw material testing requirements under GMP for *biologic drugs* includes testing of each batch of raw material and compliance with specifications for that raw material (C.02.009 and C.02.010).[32] Health Canada confirmed that there is no separate regulations for autologous versus allogeneic products under the FDR.

4.4.2. Active substances

Active substance often correlates with starting materials and the final product for advanced therapies. Therefore, requirements for active substance are described throughout section 4.4 (section 4.4.1, 4.4.4, 4.4.5).

4.4.3. Excipients and processing aids

For cell therapy products, all materials of non-human or non-animal origin, excipients, and processing aids need to be controlled and qualified to minimize cell processing risks. They need to be tested according to an established standard to 1) confirm the identity of the materials, 2) confirm characteristics to ensure sufficient output of a manufacturing process, 3) confirm that variability in materials will not alter quality of the product, 4) confirm safety. Health Canada also refers to the CTD Module 3.2.S.2.3 for more guidance. Over time, the requirements shift from safety to consistency of the cell therapy product.[7]

4.4.4. Product characterization

For cell therapy products, information on drug substance (DS) and drug product (DP) need to be provided in the CTD, even though they may overlap substantially or be entirely the same. Manufacturing processes should be accompanied with set quality measures and a range of specifications that are considered acceptable for a cell therapy product. These specifications are meant to mainly indicate safety and potency. Examples include cell viability, cell identity, cell concentration, purity and contamination.[7]

FDR sections C.02.018 and C.02.019 mandate that each batch or lot of drugs needs to be tested and characterized before release on the market.[32] In addition for quality testing each lot of *biologic drugs* needs to be manufactured according to the practices on which the product was approved to ensure product consistency.[10] Compared to biologic drugs and drugs there is flexibility in the exact time points that cell therapy products need to be tested. As such, not all tests may be required at the point of manufacturing DS versus DP.[7]

Health Canada recognized that the development of cell therapy product specifications may be difficult in early stages of clinical trials due to potential gaps in preclinical data. Consequently, safety specifications are acceptable in earlier phases, while in later phases of clinical trials specifications need to demonstrate a link to clinical outcomes, in particular specifications of potency.[7]

4.4.5. Manufacturing

GMP

All pharmaceuticals, biologics, radiopharmaceuticals, and veterinary drugs are regulated under Division 2 to ensure GMP. Health Canada has harmonized its regulation of GMP with international standards of the World Health Organization, the Pharmaceutical Inspection Cooperation/Scheme and the ICH.[32] Standard GMP aspects such as equipment, sanitation, raw material testing, quality control and stability are regulated under Division 2 of the FDR.

Health Canada has separate guidelines to facilitate GMP compliance for *biologic drugs*.[10] The different sections provide guidance to an approach for GMP compliance that takes the product characteristics of *biologic drugs* into account, such as specific biologic analytical techniques for quality control. However, due to specific characteristics of advanced therapies it is acknowledged that these GMP guidelines for *biologic drugs* cannot always be directly applied to advanced therapies. Health Canada indicated that these guidelines for GMP compliance for *biologic drugs* do provide an indication on the needed requirements for manufacturing and quality for advanced therapies. Exact manufacturing and quality requirements for advanced therapies are determined on a case-by-case basis by Health Canada.

GMP compliance is more stringent after marketing authorisation. Investigational products are regulated under Division 5, which requires compliance with GMP requirements under Division 2, but exempts investigational products from sections C.02.019 (product testing by labeller of drug), C.02.025 (retention of samples), C.02.026 (volume of sample).[33] These GMP regulations during development also account for advanced therapies. Interpretation of GMP guidelines during clinical development is more flexible, and stringency in GMP compliance increases between early- and late-stage clinical trials with advanced therapies.[8]

Licensing / accreditation

In order for developers to submit a NDS and to be granted marketing authorisation, manufacturers need to be licensed prior to filing (FDR, Part C, Division 1A). They can obtain an establishment license by the Health Products and Food Branch Inspectorate. Both Canadian and foreign manufacturers need to comply with GMP in order to obtain a license (FDR, Part C, Division 2). Also for advanced therapies that are regulated as *biologic drugs*, GMP compliance is required at this stage. Before approval, an on-site evaluation of the manufacturing facility and process is part of the procedure. After an establishment license is granted, annual reporting is required. Establishment licenses are granted to manufacturing sites before marketing authorisation only, after late-stage clinical trials have been completed.[8]

Batch release control

The regulation of *biologic drugs* under section C.04.015 of the FDR mandates that for each batch to be sold in Canada, a sample and protocols of testing need to be submitted to Health Canada. Sales are prohibited if protocols or samples fail the requirements. Health Canada uses a risk-based approach in its Lot Release Program to sub-divide *biologic drugs* into four classes based on investigational and post-marketing experience with the product and product characteristics. Investigational products that have not been marketed are categorized as high-risk class I products. Sponsors are required to send a notification to BGDT that needs to approve lot release administration in clinical trials. Class two to four are all products in the post-marketing phase, with risk decreasing in each group. Assigning products to these groups is decided on a case-by-case basis, including for advanced therapies. Product characteristics that are taken into account are the product indication, the nature of the product (e.g. complexity) and the product history (e.g. consistency of manufacturing). Class two products are most strictly quality controlled; each lot is tested by Health Canada before release on the market. In Class three the protocols for testing are reviewed and samples can be requested for testing by Health Canada. Class four represents products with the lowest risk. Only a notification before release is required, without approval. Samples for testing can be required.[9] As only one advanced therapy has been approved, advanced therapies are most likely to be classified as group 1 (investigational), or group 2 (new drug). Laboratories that perform lot testing also need to be licensed and are subject to inspection.[8]

Contamination

Contamination is considered a key issue for cell therapy products, because many methods to prevent contamination are not suited for living cells. Raw material testing, in-process testing, and final product testing need to be included in the CTD. These controls need to be executed at different time points to determine when the adventitious agent(s) were introduced. The Risk Management Plan (RMP, see section 4.5), needs to include a strategy how to minimize the risk of infectious disease spreading and how to act if cell therapy products were administered prior to positive testing for adventitious agents.[7]

Throughout the GMP regulations, contamination and cross-contamination are of concern for all therapeutics. The FDR aims to prevent contamination by setting standards for equipment (FDR, Section C.02.005), ensure sanitation (FDR, Section C.02.007-8), and tests need to be performed to detect contamination or cross-contamination in raw materials (FDR, Section C.02.009-010). FDR section C.02.029 mandates that drugs are fabricated and packaged in facilities and methods to ensure sterility, and handled by appropriately trained personnel.[32]

Purity

Purity assays are indicated as an essential part of the product specifications in the GMP guidelines for *biologic drugs*.[32] For cell therapy products it needs to be decided on a case-by-case basis which purity assays are considered acceptable, depending on the product characteristics and the stage of processing. Impurities that can impact product quality and safety need to be able to be detected, identified, and quantified by the chosen purity assays. Health Canada refers to the international guidance ICH Q2(R1) to characterize impurities.[7]

Stability

General stability requirements are regulated under FDR section C.02.027-028, which mandate to provide evidence of product stability until expiry.[32] For biologics, stability is linked to the biologic activity and potency.[10] Even before approval this needs to demonstrated prior to administration in clinical trials. For cell therapy products, this would imply potency testing after manufacturing, following distribution, and before administration. During later stages, testing stability for different time periods and conditions can be used to determine shelf-life. No specific guidance is provided due to the variability of cell therapy products. Appropriate stability testing will be determined on a case-by-case basis.[7] In some cases guidance documents may be used from the US are used, for example for stability testing of vectors used in cell or gene therapies.[26] This additional information should provide sufficient data to support the anticipated specific targeting *in-vivo* and subsequent gene expression.[8]

Potency

Potency assays are indicated as an essential part of the product specifications in the GMP guidelines for *biologic drugs*.[32] For cell therapy products it may be difficult to determine potency assays, because the mechanism of action is often poorly understood. However, it is recommended to include a specification of cell therapy product potency when it has reached later stage clinical trials.[7]

Traceability

General requirements for manufacturing records and interpretation for *biologic drugs* are described under FDR section C.02.020-024. Under FDR section C.02.020 it is required that results of raw material testing need to be retained, records of each lot or batch need to be retained, and other record keeping in order to comply with GMP and ensure tracebility.[32]

4.4.6. Differences in manufacturing and quality requirements between autologous / non autologous products

There is no difference between manufacturing and quality standards for autologous versus allogeneic cell therapy products that are regulated under the FDR. The manufacturing and quality requirements that are described under section 4.4 apply.[2]

4.4.7. Description of processes of approval of changes in manufacturing processes of advanced therapies

Advanced therapies that are regulated as *biologic drugs* are subject to the Lot Release Programme, in which product quality is tested for each lot. Generally, lot release tests have been validated during development and include various tests and specifications to determine potency, identity, purity, sterility, and assays for contamination, among others.[34] Any inconsistencies in the processing and subsequent changes in safety and quality of the product post-marketing may lead to the re-assignment into a different risk group in the Lot Release Programme.[9] Manufacturers of products in group two to four need to provide annual information (Yearly Biologic Product Report) to BGDT under section C.01.014.5, C.08.007, and C.08.008 of the FDR.

If any changes have occurred in manufacturing, re-assignment can be based on review of the Yearly Biologic Product Report, or after manufacturers apply for re-assignment.[9] As all manufacturing sites that produce marketed products need to be licensed, the manufacturing site cannot be changed without prior agreement of Health Canada. Health Canada confirmed that post-marketing changes of all *biologic drugs*, including advanced therapies, are regulated under the Lot Release Programme.

4.5. Post-marketing requirements for advanced therapies

4.5.1. Post-marketing requirements for advanced therapies vs. chemical-based medicines

Health Canada does not have specific post-marketing requirements in place for advanced therapies. All chemical-based and *biologic drugs* need to comply with similar post-marketing requirements. These need to be specified in Risk Management Plans (RMPs), which are an essential part of a NDS.[35] Health Canada accepts foreign formats of RMPs, in particular those European Medicines Agency,[36] plus Canadian specific sections that relate to Canadian disease prevalence and patient populations. Safety follow-up recommendations can include specific pharmacovigilance activities, risk minimization activities, impact studies of risk minimization activities, and an Annual Summary Report (equivalent to Periodic Safety Update Reports in Europe). RMPs of marketed *biologic drugs* are reviewed by the Marketed Biologicals, Biotechnology and Natural Health Products Bureau.[35]

As mentioned above (see section 4.3.2), products that adhere to specific conditions that relate to unmet medical needs can be granted a Notice of Compliance with conditions (NOC/c). These products show a promising clinical benefit and acceptable safety profile, which needs to be confirmed in post-marketing studies. Sponsors need to report on progress with studies and incoming data on an annual base by sending reports to Health Canada. They also need to notify Health Canada immediately when any substantial changes in the risk-benefit profile of the product occur. Details of post-marketing requirements are agreed upon between the sponsor and Health Canada on a case-by-case basis, depending on the medicine specific uncertainties that need to be addressed. It is always required to perform enhanced post-market safety surveillance, in which adverse reaction detection methods need to be systematic (e.g. clinical trials intended to monitor safety issues and other active surveillance activities).[28]

4.5.2. Description of additional post-marketing requirements specific for advanced therapies

There are no additional post-marketing requirements in place that are specifically for advanced therapies. Currently, only one advanced product, Prochymal, has been authorized and is granted a NOC/c in Canada. The agreed conditions provide an example of additional post-marketing requirements necessary under this approval

scheme. The developer of Prochymal is required to demonstrate the positive risk-benefit profile by additional post-marketing confirmatory studies, studies specified in the RMP, and a registry for patients needs to be maintained. The specific elements of each requirement can be found in Table 4.2.

Other details of the agreement between the sponsor of Prochymal and Health Canada include a commitment to report all Adverse Reactions outside of Canada and to submit annual Periodic Safety Update Reposts (PSURs) specific to NOC/c products.[34]

Table 4.2 Specific post-marketing obligations agreed between Health Canada and the sponsor of Prochymal as part of the obtained NOC/C

Post-marketing requirements	Goal	Included specific sponsor obligations
Risk Management Plan	Support continuous positive risk/benefit profile	▪ Update Product Monograph (risk profile); ▪ Safety considerations for pregnant women; ▪ Plan for monitoring off-label Adverse Events; ▪ Information on donor screening; ▪ Ensure product traceability; ▪ Ethical conduct while dealing with donor material; ▪ Determine possible ectopic tissue development long-term.
Confirmatory study as part of NOC/C	Provide evidence of efficacy in a paediatric or steroid refractory acute Graft versus Host Disease (aGvHD) population	▪ Provide evidence of significant efficacy in a steroid refractory aGvHD population; ▪ Perform randomized controlled study designs or appropriate case control studies.
Patient registry	Enable long-term safety monitoring	▪ Maintain registry of all Prochymal treated patients (on- and off-label).

Information obtained from.[36]

4.6. Routes for patients to have access to advanced therapies outside of clinical trials and marketing authorisation

When an investigational therapeutic product, which is regulated under the Food and Drugs Act and the FDR, is not available for a patient because he or she is not enrolled in a clinical trial, an exemption for patient use may be granted through the Special Access Programme (compassionate use). The Special Access Programme is applicable to all investigational therapeutics that are regulated under the Food and Drugs Act, including advanced therapies, chemical-based drugs and *biologic drugs*.[31]

Access to investigational treatment under the Special Access Programme is granted on a case-by-case basis. It can only be granted in medical emergency situations where current standard treatment fails or when it is unsuitable or unavailable. Special Access Requests need to comply with sections C.08.010 and C.08.011 of the FDR. Main authorisation requirements are: limited sales for medical emergency use only, submission of supporting evidence for safety and efficacy, listing of all institutes where patients will be administered the therapeutic, reporting of adverse reactions, and account for all received batches by the practitioner. Other data may be required under the discretion of Health Canada (FDR, Sections C.08.010 and C.08.011).[31]

Special Access is typically granted for treatment of individual patients, not in a clinical trial setting. Instead of using Special Access, which is granted when clinical trials are already ongoing, developers are encouraged to draft plans for open label clinical trials with less strict inclusion criteria or compassionate use in the drug development plan.[31] The Special Access Programme does not assess the risk-benefit profile of an investigational therapeutic. Quality, safety and efficacy are not guaranteed by treatment authorisation under this exemption of the Food and Drugs Act and the FDR. There are no other means by which patients can have access to advanced therapies.

4.7. Views of stakeholders on the regulatory framework

The Canadian regulatory framework consists of general standards to which developers of advanced therapies need to adhere, with some specific guidance on how to interpret these general standards in the context of advanced therapy development. This approach is believed to offer both regulators and developers with the necessary flexibility to regulate a field that has a wide variety of products and is rapidly advancing.

4.7.1. Factors facilitating development and authorisation of advanced therapies in Canada

General:

- Only high-level guidance is available for the development of advanced therapies and more 'general' regulations for biologic *drugs* apply. Health Canada acknowledged that not all regulations for *biologic drugs* may be applicable to advanced therapies. Its regulatory decisions are based on a risk-benefit assessment on a case-by-case basis. Overall, Health Canada indicated to take a flexible approach while applying its regulatory framework for *biologic drugs* to advanced therapies;
- Developers are encouraged to engage with Health Canada from early development phases onwards. Overall, Canadian developers were positive about the interactions with Health Canada and the support they received in interpreting the prevalent standards. The approach of Health Canada was considered 'flexible' and 'case-by-case'. This was believed to suit the characteristics and variability of current advanced therapy development;
- Standardized practices were believed to emerge by consensus between developers in the field and Health Canada instead of a top-down approach. Moreover, uncertainties and barriers in product development such as the lack of quality standards were considered a natural state of the field and were often not specifically attributed to unclear or incomplete regulatory standards.

Specific facilitating factors that were mentioned were:

Preclinical studies:

- Animal studies can represent a large uncertainty in preclinical studies because of translation issues between species. The data requirements to start earlier phase clinical trials for advanced therapies were believed to be sufficiently flexible, taking into account the nature of individual products. A relatively small-scale preclinical animal study design with a justification why it suits the purpose of the study and product characteristics may be acceptable for a CTA, instead of large scale animal studies with multiple species.

Manufacturing and quality:

- Health Canada has an explicit policy to become more stringent about manufacturing and quality requirements as clinical development progresses. This enables flexibility in earlier phases of clinical trials when product characterization may not have been finalized entirely. Potency assays were mentioned as one of the main challenges for meeting quality requirements in early phases. Canadian developers considered Health Canada to be open for dialogue in these cases and to be cooperative to address manufacturing and quality issues with a focus on safety.

Alternative approval procedures:

- The Notice of Compliance with conditions pathway enables advanced therapies to reach the market sooner and to collect additional data post-marketing and inclusion in reimbursement schemes.

4.7.2. Factors hampering development and authorisation of advanced therapies in Canada

Some developers were uncertain about the standards they needed to adhere to and mentioned some barriers in product development. Some of the issues should be understood in light of the specifics of the advanced therapies sector in Canada, which is mainly populated by academic centres and less by pharmaceutical companies who are generally more used to work with regulatory frameworks.

Importantly, two developers also mentioned that the biggest barrier for development of advanced therapies in Canada is not the regulatory framework, but gaps in funding in academic research, a lack of financial incentives for industrial developers and scientific challenges. The Canadian reimbursement scheme may also provide disincentives, specifically for companies to market in Canada, e.g. because reimbursement procedures are handled by the provinces. Lengthy reimbursement procedures and a relatively small market may lead to global development strategies that do not include Canada.

General:

- Compliance with GLP, GMP and GMP-like standards during pre-clinical testing and development was pointed out as difficult, particularly for developers at academic centres (see below for specifics);
- Although the policy of increased stringency through development was encouraged, it also induced uncertainties for developers about the exact requirements they need to adhere to for a CTA;
- The lack of technological product refinement to ensure positive benefit-risk profiles was mentioned as an important barrier to reach product approval. Clinical trial study design refinement is also needed to resolve issues such as a lack of statistical power when patient populations are small.

Preclinical studies:

- Compliance with GLP was indicated to create high costs for developers at academic centres. Moreover, if cell processing changes over time, more animal data may be required. In general, collecting data from animal studies and other data needed for a CTA were referred to as challenging (see also section 4.7.1);

- Collecting data to support a mechanism of action (potency assays) and safety concerns such as tumourigenicity in a CTA were indicated as particularly burdensome.

Manufacturing and quality:

- Developers indicated to have a poor understanding of GMP standards. It was mentioned to be challenging to develop protocols that reach satisfactory manufacturing and quality standards. To date, there are no specific manufacturing and quality standards in place for advanced therapies. Instead, manufacturing and testing protocols need to be determined on a case-by-case basis during development. Less rigorous GMP requirements for a CTA and increased stringency through development was believed to offer flexibility. However, it also creates uncertainties for developers about the exact requirements they need to adhere to;
- Compliance with GMP or even GMP-like standards during development was perceived to be very costly, particularly because of the required documentation. The lot testing and release procedures were also mentioned to be burdensome, particularly for developers of autologous products. Even though a procedure and specifications for testing may be established, under the lot testing and release requirements, each treatment for each individual patient represents a lot and needs to be tested rigorously. The regulatory framework is a direct cause for high treatment costs because of this requirement.

Clinical trials:

- Advanced therapies that are developed by academic centres are regulated under the same framework as medicines developed by pharmaceutical companies. Academic developers mentioned that they did not consider this standard drug approval pathway (i.e. phase I to phase III trials) fit-for-purpose for the development of advanced therapies within academic centres due to the fundamentally different characteristics of advanced therapies (typically produced for small patient populations in small volumes) compared to chemical-based drugs (typically produced for large patient populations in large volumes). Thus, the standards that are in place for large phase III trials in particular impose challenges for advanced therapies. Developers also indicated that the electronic submission tools for clinical trials that are available are not tailored to their needs, which creates many uncertainties as to what is applicable in the preparation of a CTA.

Other uncertainties:

- No policies or regulations in Canada explicitly address autologous cell therapy products yet. Decisions therefore need be made on a case-by-case basis that take into account jurisdictional responsibilities.

4.8. References

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5. Analysis of the regulatory framework governing advanced therapies in Japan

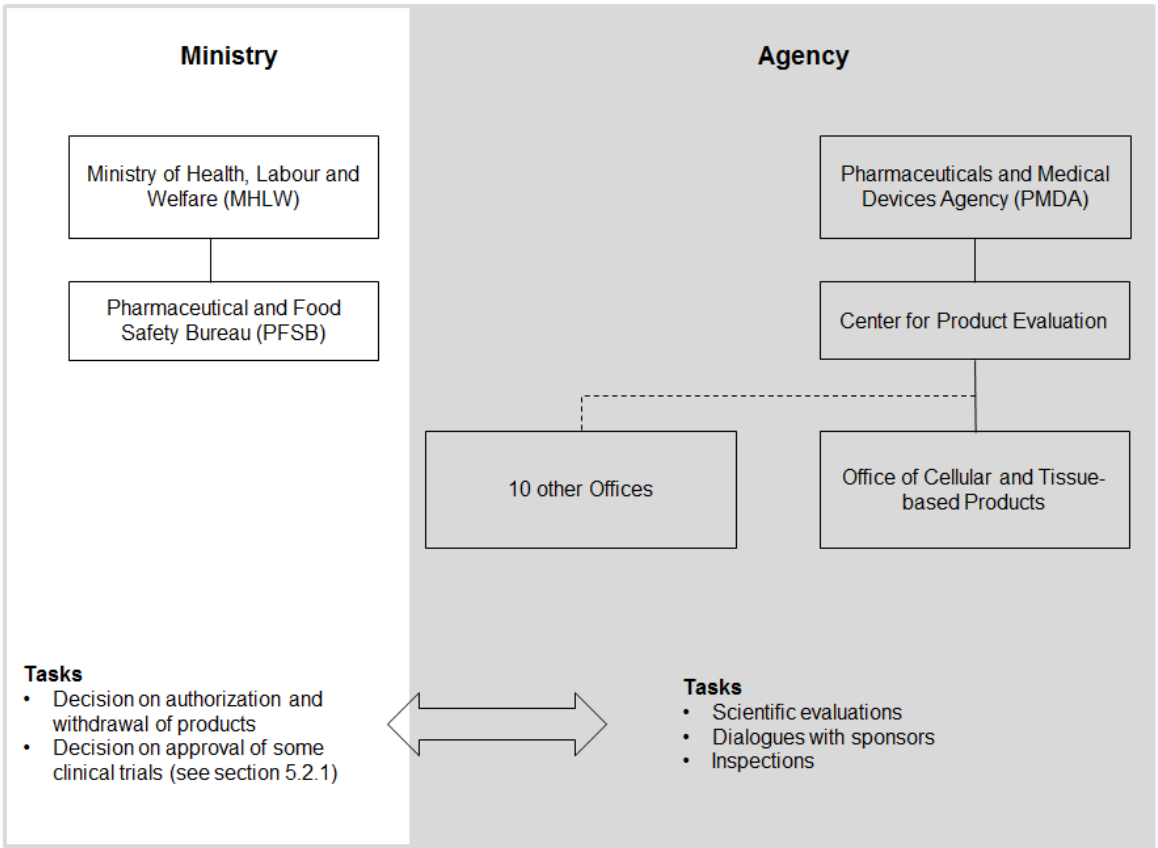
5.1. Overview of regulatory framework for advanced therapies in Japan

5.1.1. Regulatory responsibilities and mandate

The regulatory responsibilities for medicinal products in Japan are distributed over two agencies. The Ministry of Health, Labour and Wealth (MHLW) bears final responsibility for providing marketing authorisation to medicinal products and has the authority to issue safety warnings or withdraw products following safety concerns. Within the MHLW, the Pharmaceutical and Food Safety Bureau (PFSB) is responsible for the regulation of pharmaceuticals.

The Pharmaceuticals and Medical Devices Agency (PMDA) is the executive and operational agency that implements and oversees regulations. Tasks include the conduct of scientific reviews, consultations with sponsors and inspections of laboratory, manufacturing and clinical facilities. Within the PMDA, the Office of Cellular and Tissue-based Products (OCTP) is responsible for regulating advanced therapies (see Figure 5.1).[1] Several other offices within the PMDA are responsible for chemical-based drugs (Offices of New Drug I-V).[2]

Figure 5.1 Agencies involved in the regulation of advanced therapies in Japan



5.1.2. Description of general regulatory framework for advanced therapies

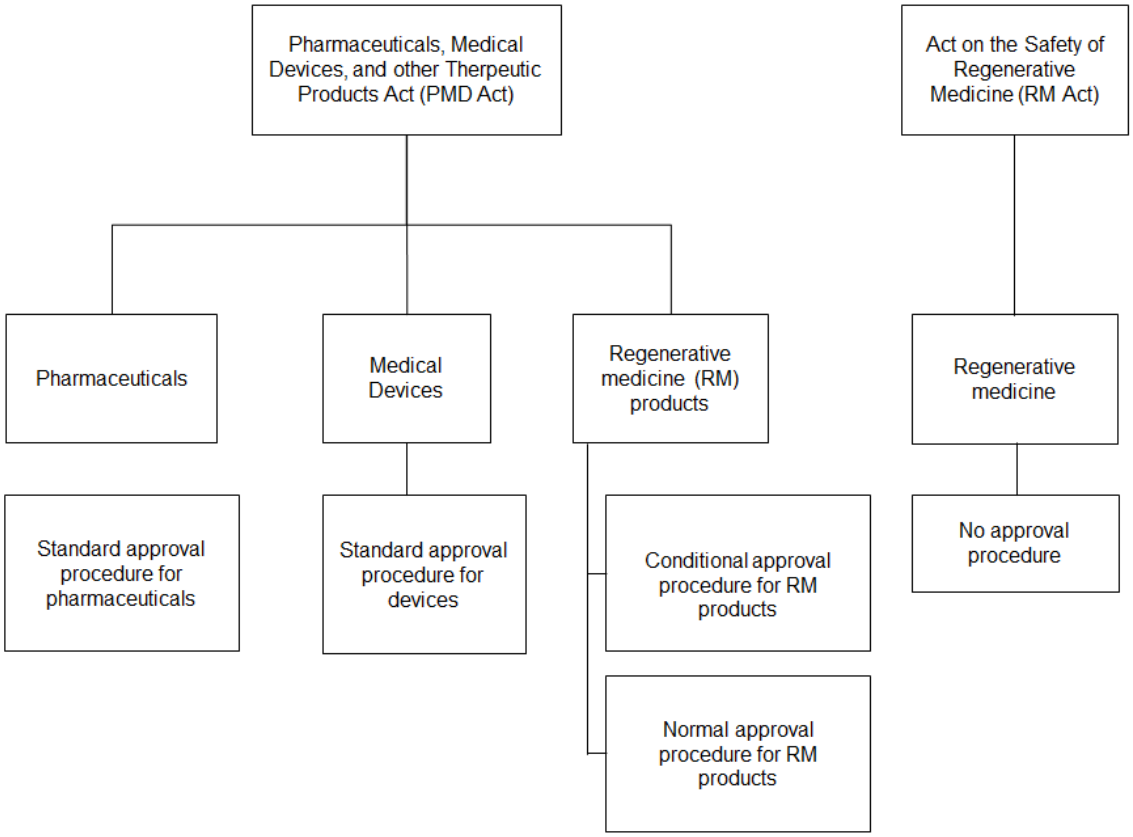
The Japanese regulatory framework operates on several levels consisting of national Acts and two-levels of legally-binding regulations that implement these acts: cabinet (government) ordinances and ministerial ordinances. The relation between the Acts and regulations is hierarchal: ministerial ordinances need to follow cabinet ordinances, and cabinet ordinances need to follow acts. Non-binding guidelines may be implemented through publication of a notification letter by a regulatory authority.[3] Some standards may also be specified in laws and/or ordinances such as is the case for GCP.

In 2013, the *Regenerative Medicine Promotion Law* was passed to promote the development of advanced therapies in Japan. The Act specified the development of two other Acts to regulate advanced therapies: the *Act on the Safety of Regenerative Medicine* (RM Act) and the *Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act* (PMD Act) which is a revision of the former *Pharmaceutical Affairs Law* (PAL).[4] The acts were enacted in November 2014 and form the primary basis of the current regulatory framework for advanced therapies in Japan.[5]

The two acts specify two different pathways through which patients can get access to advanced therapies. The RM Act regulates experimental research conducted with *regenerative medicine* at medical centres in cases where efficacy has not yet been established. Clinical research covered under the RM Act is typically performed in medical institutions for academic purposes and cannot be part of a marketing authorisation procedure.[6] This type of research falls under the direct responsibility of the MHLW. As clinical research on *regenerative medicine* was previously regulated as daily medical practice under the Medical Care Act and Medical Practitioners Act, the RM Act enhances regulation with respect to safety and ethical issues.[7] The PMD Act regulates the development of *regenerative medicine products* for marketing authorisation. This development pathway is overseen by the PMDA (see section 5.1.3 for definitions).[6]

The PMD Act has a separate section for *regenerative medicine products*.[8] This section stipulates a regulatory pathway for marketing authorisation that consists of a conditional limited-term marketing authorisation and a second approval procedure to confirm the positive benefit-risk profile after seven years (section 5.3). This pathway is exclusively designed for the authorisation of *regenerative medicine products* and cannot be used for the approval of *pharmaceuticals* and *medical devices* under the PMD Act. Figure 5.2 provides an overview of the framework.

Figure 5.2 Overview of regulatory framework and relevant marketing authorisation procedures for pharmaceuticals, devices, regenerative medicine products and regenerative medicine



The legal documents that are relevant for the regulation of advanced therapies under the PMD Act and RM Act are published by the Japanese government in Japanese only. Therefore, the references in this document do not specifically refer to these original documents, but to secondary sources that cite and/or quote the original documents. An overview of relevant cabinet ordinances, ministerial ordinances, ministerial notifications, and administrative notifications under the PMD and RM act are provided in Table 5.1.

Table 5.1 Overview of specific quality, safety, and efficacy regulations and guidelines for *regenerative medicine products* (PMD Act) and *regenerative medicine* (RM Act). Adapted from Maeda et. al 2015 (pg. 161-162),[8] and Azuma 2015[6] [all in Japanese

PMD Act	RM Act
Regulations (cabinet ordinance, ministerial ordinance and ministerial notifications)	
Revised cabinet ordinance for the enforcement of the PMD Act - 1961 Cabinet Ordinance No. 11 revised by 2014 Cabinet Ordinance No 269 (July 31, 2014).	[cabinet ordinances for RM Act]
Revised cabinet ordinance for user fees related to the PMD Act - 2005 Cabinet Ordinance No. 91 revised by 2014 Cabinet Ordinance No 269 (July 31, 2014).	[ministerial ordinances for RM Act]
Revised ministerial ordinance for the enforcement of the PMD Act – 1961 Ministerial Ordinance No. 1 revised by 2014 Ministerial Ordinance No. 87 (July 31, 2014) and PFSB Director Notice 0806 No. 3 (August 6, 2014).	Guideline for Human Stem Cell Therapy Clinical Research (Ministerial Notification of MHLW; 2006 No. 425; 3 July 2006)

PMD Act	RM Act
Revised ministerial ordinance for user fees related to the PMD Act – 2000 Ministerial Ordinance No. 63 revised by 2014 Ministerial Ordinance No. 87 (July 31, 2014) and PFSB Director Notice 0812 No. 35 (August 12, 2014).	
Standards for Biological Materials (2003 Ministerial Notification No. 210 revised by 2014 MN No. 375 (September 26, 2014) and PFSB Director Notice 1002 No. 27 (October 2, 2014).	
Good, gene, Cellular and Tissue-based product manufacturing Practice (GCTP) (Ministerial Ordinance No. 93, 2014; PFSB Director Notice 0812 No. 11; August 12, 2014; Compliance Division Director Notice 1009 No. 4 (October 9, 2014)).	
Good laboratory practice (GLP) (Ministerial ordinance No. 88, 2014; PFSB Director Notice 0812 No. 20; August 12, 2014; ELD Director Notice 1121 No. 9, and MRED Director Notice 1121 No. 13 (November 21, 2014)).	
Good clinical practice (GCP) (Ministerial ordinance No. 89, 2014; PFSB Director Notice 0812 No. 16; August 12, 2014; MRED Director Notice 1121 No. 3 (November 21, 2014)).	
Good post-market study practice (GPSP) (Ministerial ordinance No. 90, 2014; PFSB Director Notice 0812 No. 23; August 12, 2014, MRED Director Notice 1121 No. 7 (November 21, 2014)).	
Good quality practice (GQP) (Ministerial ordinance No. 87, 2014; PFSB Director Notice 0812 No. 11; August 12, 2014).	
Good vigilance practice (GVP) (Ministerial ordinance No. 87, 2014; PFSB Director Notice 0812 No. 1; August 12, 2014).	
Regulations for buildings and facilities (Ministerial ordinance No. 87, 2014; PFSB Director Notice 0812 No. 1; August 12, 2014).	
Guidelines (administrative notifications)	
General Principles for the Handling and Use of Cells/Tissue-Based Products (PFSB/MHLW Notification No. 1314 Appendix 1 – 2000).	
Quality and Safety Assurance of Pharmaceuticals Manufactured Using Human or Animal derived Components as Raw Materials (Notification of Pharmaceutical and Medical Safety Bureau, the Ministry of Health and Welfare; Iyaku-hatsu No. 1314; 26 Dec, 2000).	
Considerations in Standards for Biological Materials Notification of Evaluation and Licensing Division, Safety Division, Compliance and Narcotics Division and Blood and Blood Products Division, Pharmaceutical and Medical Safety Bureau, MHLW; Iyakushin-hatsu No. 0520001, Iyakuan-hatsu No. 0520001, Iyakukanma-hatsu No. 0520001 & iyakuketsu-hatsu No. 0520001; 20 May 2003).	
Guidance on designation of biological products and regenerative medicine products (ELD Director Notice 1105 No. 1 and MRED Director Notice 1105 No. 2, (November 5, 2014).	
Guidance on clinical trial notification (PFSB Director Notice 0812 No. 26 and MRED Director Notice 0812 No. 1 (August 12, 2014).	
Guidance on adverse event reporting during clinical trial (PFSB Director Notice 1002 No. 23 and MRED Director Notice 1002 No. 1 (October 2, 2014).	
Guidance on application for marketing authorisation (PFSB Director Notice 0812 No. 30 and MRED Director Notice 0812 No. 5 (August 12, 2014).	
Guidance on drug master file (ELD Director Notice 1117 No. 3 and MRED Director Notice 1117 No. 1 (November 17, 2014).	
Guidance on data integrity inspection (MRED Director Notice 1121 No. 11 (November 21, 2014).	

PMD Act	RM Act
Guidance on GCTP/GQP/regulations for buildings and facilities Compliance Division Director Notice 1009 No. 1 (October 9, 2014).	
Guidance on package insert/instruction for use (PFSB Director Notice 1002 No. 12 and Safety Division Director Notice 1002 Nos. 9 and 13 (October 2, 2014).	
Guidance on post-market adverse event reporting (Safety Division Director Notice 1002 No. 17 (October 2, 2014).	
Guidance on periodic infectious disease surveillance reports (PFSB Director Notice 0812 No. 7 (August 12, 2014) and Safety Division Director Notice 1113 No. 4 (November 13, 2014).	
Subgroup- or product-specific guidelines (administrative notifications)	
Guideline for Quality and Safety Assurance of Pharmaceuticals and Medical Devices Based on Human Autologous Cells or Tissue (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushokuhatsu No. 0208003; 8 Feb 2008).	Related to Operation of Guideline for Human Stem Cell Therapy Clinical Research (Notification of Health Service Bureau, MHLW; Ken-hatsu No. 0703003; 3 Jul. 2006)
Q&A on Guideline for Quality and Safety Assurance of Pharmaceuticals and Medical Devices Based on Human Autologous Cells or Tissues (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; 12 Mar 2008).	Q&A on “Guideline for Human Stem Cell Therapy Clinical Research” (Specific Disease Control Division, Health Service Bureau, MHLW)
Concepts for Manufacturing Control and Quality Control of Pharmaceuticals and Medical Devices Based on Human Autologous Cells or Tissues (Notification of Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW; Yakushokukanma-hatsu No. 0327025; 27 Mar 2008).	Processes for Human Stem Cell Therapy Clinical Research (Report for HSC, MHLW; 18 May 2006)
Guideline for Quality and Safety Assurance of Pharmaceuticals and Medical Devices Based on Human Allogeneic Cells or Tissues (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0912006; 12 Sep 2008).	Processes for Evaluation of Human Stem Cell Therapy Clinical Research Based on “Guideline for Human Stem Cell Therapy Clinical Research” (Report for HSC, MHLW; 27 Jul. 2006)
Q&A on Guideline for Quality and Safety Assurance of Pharmaceuticals and Medical Devices Based on Human Allogeneic Cells or Tissues (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; 3 Oct 2008).	
Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Autologous Human Somatic Stem Cells (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-2; 7 Sep 2012).	
Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Allogeneic Human Somatic Stem Cells (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-3; 7 Sep 2012).	
Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Human (Autologous) Induced Pluripotent Stem-Like Cells (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-4; 7 Sep 2012).	
Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Human (Allogeneic) Induced Pluripotent Stem-Like Cell (Notification of	

PMD Act	RM Act
Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-5; 7 Sep 2012).	
Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Human Embryonic Stem (ES) Cells (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-6; 7 Sep 2012).	

5.1.3. Regulatory framework for advanced therapies

Advanced therapies may be regulated under the PMD Act or the RM Act depending on whether the developer aims to obtain market authorisation or conducts (academic) clinical research not intended for marketing authorisation, respectively. This subdivision essentially creates two legal definitions of advanced therapies in Japan: a definition of *regenerative medicine products* in the PMD Act and *regenerative medicine* in the RM Act. In short, the definition of *regenerative medicine products* closely adheres to the definition of advanced therapies in this report. However, academic research with *in-vivo* gene therapy is not in the scope of the RM Act, instead it is regulated under the Medical Care Act and Medical Practitioners Act. *In-vivo* gene therapy for market authorisation is within the scope of the PMD Act. Product definitions are provided in Table 5.2.

Table 5.2 Definitions of advanced therapies in the PMD Act and RM Act

Product type	Definition
Regenerative medicine products (PMD Act, Article 2(9))	1. Processed human or animal cells intended for either: (a) the reconstruction, repair, or formation of the structure or function of the human (or animal) body (i.e., tissue-engineered products); (b) the treatment or prevention of human (or animal) diseases (i.e., cellular therapy products). 2. Articles intended for the treatment of disease in humans (or animals) and are transgened to express in human (or animal) cells (i.e., gene therapy products)[3,6].
Regenerative medicine (RM Act)	Processed human or animal cells: 1. that are intended to be used for: (a) the reconstruction, repair, or formation of the structure or function of the human body; or (b) the treatment or prevention of human diseases; and 2. that are designated in the Cabinet Ordinance:[6] Among those using processed cells, the medical technology other than the following technologies: a) Transfusion of using processed cells (except those using the blood cell component made from blood cell components or human or animal cells with manipulation of changing its properties.), such as RBC, platelets, WBC; b) Hematopoietic stem cells transfusion under the Act on Appropriate provision of hematopoietic stem cell transplantation (except for hematopoietic stem cells with the manipulation of changing its properties); c) Medical technology that uses processed sperm or unfertilized egg.
Drug (PMD Act, Article 2(1))	1. Substances listed in the Japanese Pharmacopoeia; 2. Substances (other than quasi-drugs and regenerative medicine products), which are intended for use in the diagnosis, treatment, or prevention of disease in humans or animals, and which are not equipment or instruments, including dental materials, medical supplies, sanitary materials, and programs; 3. Substances (other than quasi-drugs, cosmetics or regenerative medicine products) which are intended to affect the structure or functions of the body of humans or animals, and which are not equipment or instruments.[13]

Product type	Definition
Medical Device (PMD Act, article unknown – provided by PMDA)	The machinery (except regenerative medical products) intended for the diagnosis of disease in humans or animals, or for treatment or prevention of disease, or for affecting the structure or function of the body etc., that refers to those specified by a Cabinet Order.

5.1.3.1. Identification of classes regulated as advanced therapies under the PMD Act

Advanced therapies are regulated *as regenerative medicine products* under the PMD Act. These products are defined in Article 2(9) of the PMD Act:

- *"Processed human or animal cells intended for either:*

  (c) the reconstruction, repair, or formation of the structure or function of the human (or animal) body (i.e., tissue-engineered products);

  (d) the treatment or prevention of human (or animal) diseases (i.e., cellular therapy products).

- *Articles intended for the treatment of disease in humans (or animals) and are transgened to express in human (or animal) cells (i.e., gene therapy products)".* [3,6]

In addition to the general definition, the cabinet ordinance of the PMD Act (PMD Act, Article 1-2) specifies three subtypes of products that qualify as *regenerative medicine products* under the PMD Act:[6]

- *"Processed human cell products, such as iPS cell-derived products, embryonic stem (ES) cell-derived products or somatic cell products;*
- *Processed animal cell products;*
- *Gene therapy products".*

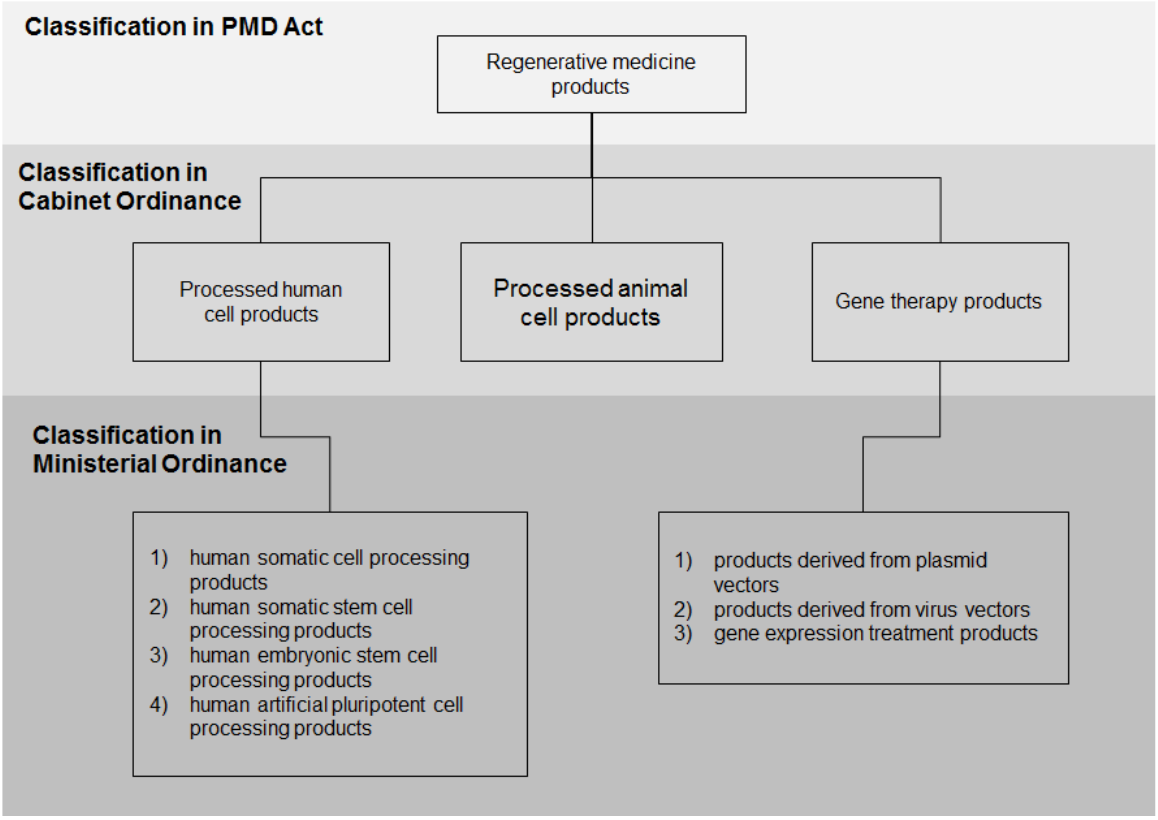
Human cell products and animal cell products are not further defined in the PMD Act, but treatment in humans with any processed human or animal-derived cells is considered a 'cell therapy'.[8] Moreover, the ministerial ordinance of the PMD Act specifies which processed human cells are specifically regulated:[9]

- *"human somatic cell processing products;*
- *human somatic stem cell processing products;*
- *human embryonic stem cell processing products;*
- *human artificial pluripotent cell processing products".*

Processing is defined under the PMD Act as:

- *"artificial expansion/differentiation of cells;*
- *establishment of a cell line;*
- *chemical treatment to activate cells or tissues;*
- *modification of biological characteristics;*
- *combination with noncell/non-tissue components; and/or*
- *genetic modification of cells conducted for the purpose of treatment of diseases or for repair or reconstruction of tissues."*[8]

Figure 5.3 Definition of regenerative medicine products in PMD Act and its cabinet and ministerial ordinances



In addition, the PMDA indicated that additional aspects are included under the definition of processing:

- isolation/separation of specific cells by biological and chemical treatment with agents;
- cells for non-homologous use.

These aspects are considered *processing* regardless of cell line development.

Gene therapy is defined as the introduction of genes into the human body, or the introduction of genes into extracted human cells that are transplanted back into the human body.[6] Both in-vivo and ex-vivo gene therapy using viral or non-viral vectors are included under the PMD Act. Products that contain unmodified viruses are not considered gene therapy products (e.g. vaccines, siRNAs).[8] The ministerial ordinance of the PMD Act specifies which gene therapy products are included:[9]

- "products derived from plasmid vectors;
- products derived from virus vectors;
- gene expression treatment products".

Platelets originating from induced Pluripotent Stem (iPS) cells are regulated as *regenerative medicine products* as well.[6]

Products exempted from the requirement to obtain marketing authorisation under the PMD act

All *regenerative medicine* and *regenerative medicine products* that do not adhere to the definition of *processing* are excluded from the PMD Act and RM Act. *Processing* does not include the following:

- "separation and cutting of tissues;
- isolation of specific cells (except for isolation following biological/chemical treatments);
- treatment with antibiotics;
- washing;
- sterilization by gamma ray;
- freezing;
- thawing, and/or other procedures that do not use cells for the purpose of gaining different structures and functions from the original cells." [3,8,10]

This minimal level of *processing* is similar to minimal manipulation as referred to in this report and defined in the Canadian and US regulatory framework. Advanced therapies require more-than-minimal manipulation. Hence, all gene-, cell- and tissue-based products that are minimally *processed* as defined in the Japanese legislation are not advanced therapies and are also not regulated under either the RM Act or PMD Act. Furthermore, the PMDA indicated that *processing* includes cells for non-homologous use. Thus, unprocessed cell therapies that are intended for non-homologous use are regulated as *regenerative medicine products*. This also accounts for *regenerative medicine* regulated under the RM Act.

Organ transplantation is excluded from the PMD Act.[8] Products such as human red blood cells, hematopoietic stem cells grafts, and fertilized embryos for reproductive assistance medical care are not considered *regenerative medicine products* and hence no marketing authorisation is necessary.[9] However, the PMDA indicated that (1) hematopoietic stem cell transfusion can be regulated under the PMD Act if the extent of non-homologous use is deemed sufficient. Hematopoietic stem cell transfusion for homologous use (2) is regulated under the Act on Appropriate provision of hematopoietic stem cell transplantation. (3) Plasma-derived products and other blood products are always exempt from the Regenerative Medical Product Chapter of the PMD Act, and are regulated as *pharmaceuticals*. Other product classes that do not adhere to the definition of *regenerative medicine products* are dental plates, artificial joints, attenuated live vaccines, and antisense oligonucleotides, among others.[9] These product classes may be regulated as *pharmaceuticals* or *medical devices*.

5.1.3.2. Identification of classes regulated as advanced therapies under the RM Act

The RM Act was enacted to regulate (academic) clinical research with *regenerative medicine* not intended for marketing authorisation. The goal of the act was to both enhance patient access and increase safety of regenerative medicine in research-settings.[8] To be considered a *regenerative medicine* under the RM Act, therapies need to be *processed*.

The definition of *regenerative medicine* in the RM act is largely similar to the definition of *regenerative medicine products* under the PMD Act. The same definition for *processing* is used for both the RM Act and the PMD Act. However, there is one notable difference between the PMD Act and the RM Act. *In-vivo* gene therapy is

excluded from the RM Act. The PMDA indicated that these are regulated under the Medical Care Act and Medical Practitioner Act. *Ex-vivo* gene therapies are included in the definition of *regenerative medicine* under the RM Act as mentioned in the Cabinet Ordinance.

For research purposes, the cabinet ordinance no. 278 of the RM Act defines that blood products, hematopoietic stem cell transplantation, reproductive medicine, and organ and tissue transplantations do not need to comply with the RM Act.[6]

5.1.4. Description of methods to control advanced therapies without therapeutic indication

The PMDA indicated that if cosmetic products adhere to the definition of *regenerative medicine product* the product has to (1) target the reconstruction, repair, or formation of structures or functions of the human body, or (2) target the treatment or prevention of human diseases. Invasive surgeries that use human skin graft for cosmetic purposes will be regulated under the PMD Act or RM Act, depending on the purpose of the surgery. Cosmetic cell-based products are expected to require an individual marketing authorisation under the PMD Act.

5.2. Framework governing clinical trials with advanced therapies

The Japanese regulatory framework distinguishes between the activity of 'clinical research' and 'clinical trials'. 'Clinical research' is conducted under the RM Act, while 'clinical trials' are conducted under the PMD Act. 'Clinical research' is conducted to gain scientific knowledge and determine appropriate medical techniques. In contrast, 'clinical trials' covered under the PMD Act have the purpose to advance to a marketing authorisation.[8] The standards for application and conduct of 'clinical research' and 'clinical trials' differ as further outlined below.

5.2.1. Responsible parties and tasks for clinical trial authorisation and supervision

Supervision and authorisation of clinical research under the RM Act

Applicable standards for the conduct of 'clinical research' under the RM Act, depend on the level of risk. *Regenerative medicine* are divided into three classes (Figure 5.4):[7] Class I (high risk) includes high risk *regenerative medicine*, including induced pluripotent stem cells (iPS) or embryonic stem cells (ES), transgened cells, and allogeneic cells. Class II (moderate risk) includes mostly non-homologous stem cell therapies, for example autologous mesenchymal stem cells. Class III (low risk) includes cell therapies for treatment that do not qualify as class I or II, or are not based on stem cells or on non-homologous cells.[6]

Figure 5.4 Decision tree to categorize regenerative medicine by risk class

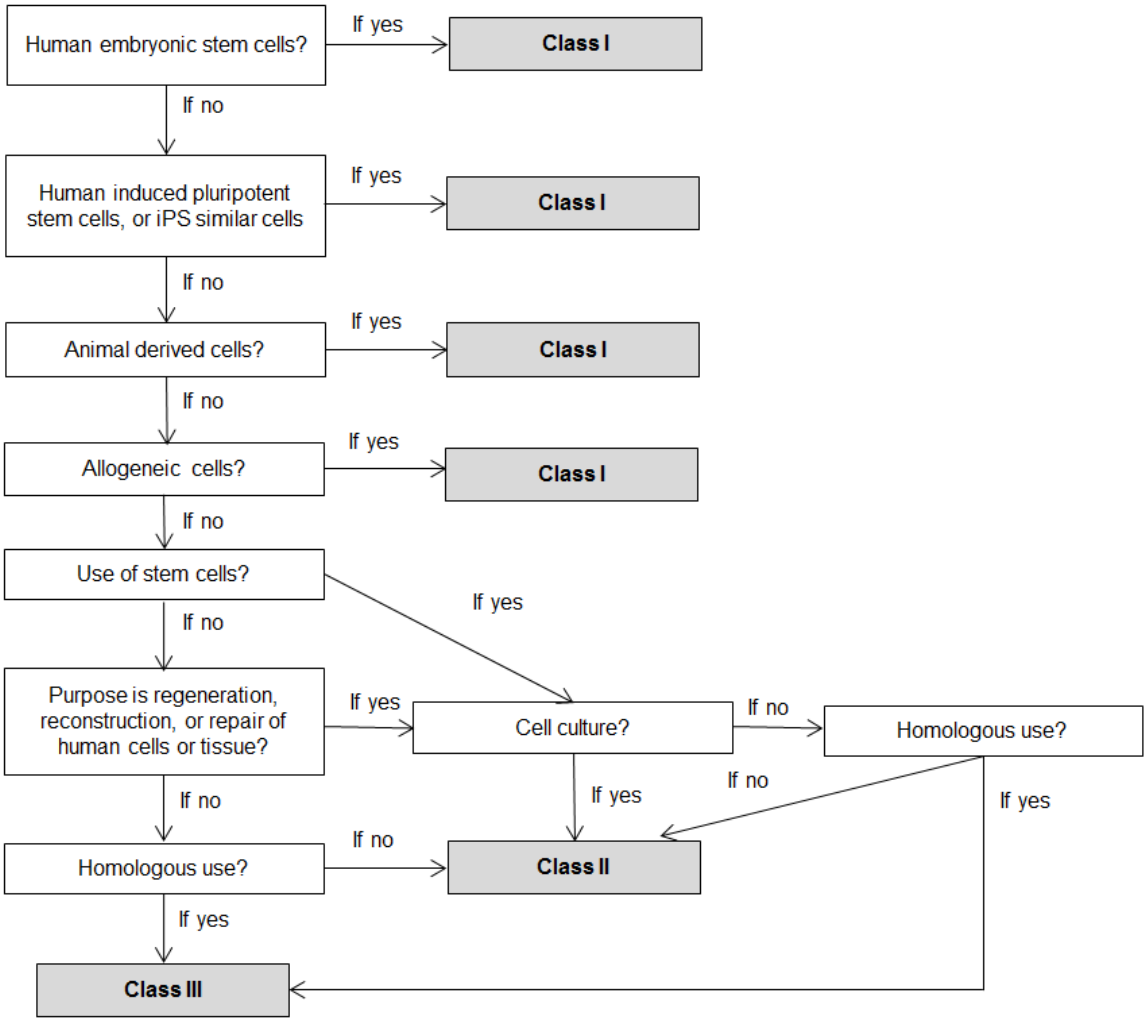


Figure adapted from MHWL[22]

For all risk classes of *regenerative medicine*, investigators need to submit a cell provision plan (notification) to a certified committee. The PMDA indicated that the cell provision plan needs to include a description of the processed cells, informed consent procedures for donors and recipients, research related to similar treatments and/or similar processed cells, quality control documents, summary of provision plan, contract with external processing facilities and privacy protection provision. If it concerns an application for off-label use under the RM Act (see section 6), the label of the marketed product needs to be included as well. The PMDA indicated that cell provision plans do not include any information on the number of patients that will be treated or the duration for which they will be treated for example (see section 5.6 for the scope of the RM Act). It is the responsibility of the certified committees to approve the provision plan.

The certified committee functions as an Institutional Review Board and may be located within or outside a medical institution. For the lowest risk class III a committee for *regenerative medicine* evaluates the provision plan. Members in this committee need to have technical knowledge about regenerative medicines.[7] For risk class I and II a *special* committee for *regenerative medicine* evaluates the provision plan. Members of

this committee need to have both technical knowledge about *regenerative medicine* as well as experience with reviewing these products.

After approval of the protocol by the respective committee, the committee either requests a formal approval procedure at MHLW (for high-risk class I) or sends a notification to the MHLW (for medium and low-risk class II-III). Moreover, the Health Science Council (HSC) provides an additional expert opinion to the MHLW for risk class I *regenerative medicine*. Taking the expert opinion of the HSC into account, the MHLW may approve the 'clinical research' protocol within 90 days.[7] Thus, only for high risk class I *regenerative medicine* an approval by the MLHW is needed to allow administration to patients in 'clinical research', while for medium and low risk-class II-III an approval by a committee is necessary, but MHLW only needs to be notified of this approval.

Investigators also need to adhere to other specifications of the RM Act when conducting 'clinical research'. This includes regulations for informed consent procedures, privacy protection, record retention, reporting of and reporting of serious adverse events. Investigators also need to send annual reports to the certified committees for regenerative medicines and the MHLW which includes information on 1) the number of treated patients, 2) disease or disability incidence as a result of clinical research, 3) an evaluation of safety and acceptability.[8]

It is not necessary for 'clinical research' under the RM Act to fully adhere to Japanese good clinical practice (J-GCP). Instead a Provider Rule is in place (RM Act Articles 3-25).[6] This implies that 'clinical research' is not subject to inspections by the regulatory authorities and compliance is solely the responsibility of the sponsor. It also implies that results obtained through 'clinical research' cannot be used for marketing authorisation procedures.[6]

Although RM sites are not subject to inspections, the Japanese authorities can verify clinical setting in which clinical research is conducted. The MHLW may also issue an administrative order to change the provision plan in case of safety concerns. If the applicant does not respond to the administrative order, the MHLW can decide to stop the 'clinical research'. The RM Act also mandates compensation by medical institutions in case of damages from experimental *regenerative medicine*.[7]

Supervision and authorisation of clinical trials under the PMD Act

Before conduct of a 'clinical trial' with a *regenerative medicine product* under the PMD Act, a Clinical Trial Notification (CTN) needs to be submitted to the MHLW. A CTN includes a clinical protocol, an investigators brochure (containing an overview of relevant available product characteristics and pre-clinical data), and informed consent materials.[8] The PMDA reviews the CTN over a period of 30 days (PMD Act Article 80-2).

Due to the complexity of *regenerative medicine products*, a sponsor is required to engage in a Pharmaceutical Affairs Consultation on R&D strategy with the PMDA before it can apply for a CTN.[6] Before filing a CTN, it is also recommended to engage with the OCTP of the PMDA to ensure that sponsors adhere to all quality and safety standards, which are specified in the relevant guidelines (see Table 5.1).[8]

When submitting a CTN sponsors are encouraged but not mandated to follow the quality sections of the Common Technical Document (CTD) format of the ICH as much as possible, even though this may not be fully possible due to the specific characteristics of *regenerative medicine products*. To be able to interpret these general CTD sections for *regenerative medicine products*, specific guidelines are in

place for different types of 'cell therapies', such as iPS cells, and autologous and allogeneic somatic stem cells (see Table 5.1).

The PMDA then evaluates safety and quality of products on a case-by-case basis with specific emphasis on product characteristics (e.g. CMC) and pre-clinical data.[6] Quality assurance is important for safety assessment of preclinical research. A Japanese developer indicated that product characteristics are considered an important indicator of potential adverse events by PMDA. For example, immature cells may differentiate in undesirable populations or become tumourigenic.

A Japanese developer also indicated that requirements for quality and manufacturing aspects become increasingly stringent as development progresses (see section 5.4). Full compliance with GCTP is not required during 'clinical trials',[9] however, developers take GCTP into account throughout the development process.

Clinical trials involving *regenerative medicine products* have to comply with Japanese good clinical practice (J-GCP) and local implementation of International Conference on Harmonization (ICH)-GCP[11] standards.[8] J-GCP adheres to the most recent ICH-GCP standards.[11]

There are also additional national specific requirements included in J-GCP. For example, each site will need its own IRB and the site head (i.e. chief executive officer of a medical institution) has more responsibilities in J-GCP than in ICH-GCP standards, including to obtain IRB approval.[12]

Compliance with good clinical practice standards also requires the review by an Institutional Review Board (IRB)/Independent Ethics Committee before the initiation of a clinical trial.[11] Consistent with GCP, clinical trials of *regenerative medicine products* are subject to inspection by the PMDA.

5.3. Framework governing commercialisation of advanced therapies

5.3.1. Approval procedures for advanced therapies under the PMD Act

Japan has introduced a marketing authorisation procedure that is exclusively applicable to *regenerative medicine products* (Figure 5.3). Sponsors that prepare a 'submission dossier' are required to demonstrate evidence of quality and safety of the product, plus demonstration of probable efficacy, in order to obtain a conditional and time-limited approval for their product (Article 23-26 of PMD Act).[6] There are guidelines in place to ensure quality and safety aspects of *regenerative medicine products* (Table 5.1). Probable efficacy can be supported with data on surrogate endpoints in relatively small patient groups (typically phase II clinical trials).

The conditional approval scheme differs from a 'standard' approval procedure for *pharmaceuticals* in that standard approval requires confirmatory data that indicates safety and efficacy on clinical endpoints (typically phase III trials).[6] Derogation from this standard for approval via the conditional approval scheme includes the possibility to use surrogate endpoints and a heterogeneous patient population in one study group to demonstrate probable efficacy. In addition, several study designs that are generally unsuited for a standard approval, including single-arm clinical trials and observational studies, may be used for the conditional approval scheme under the PMD Act, specifically to demonstrate safety of the products. Furthermore, statistical outcomes with wide significance levels may be acceptable given the less robust study designs and smaller patient populations in 'clinical trials' for *regenerative medicine products*.[9]

The PMDA decides on case-by-case basis whether the 'submission dossier' of a *regenerative medicine product* will be considered for a conditional approval procedure or a standard approval procedure (Figure 5.1). In these decisions, the PMDA takes the target disease and currently available treatment for the disease into account, plus the product-specific characteristics.[8] The conditional approval scheme exclusively applies to *regenerative medicine products*. After review of all submitted data under the conditional approval scheme, the PMDA issues Review Reports to the MHLW which then may issue a conditional approval for seven years.[7] On a case-by-case basis, the conditional approval can be restricted to specific medical institutions or physicians who have relevant expertise and training that are exclusively allowed to administer the *regenerative medicine product*.[5]

Once conditional approval is obtained, sponsors are required to perform large post-marketing clinical studies (typically phase III trials) to confirm safety and efficacy together with other post-marketing safety measures.[6] In determining post-marketing requirements, possible heterogeneity in quality aspects of *regenerative medicine products* are taken into account (section 5.5).[8]

After seven years, a sponsor needs to re-apply for a market authorisation by submitting an 'application dossier' to the MHLW. The dossier should contain additional confirmatory safety and efficacy data that was collected during the conditional approval period.[7] The MHLW then decides on a case-by-case basis whether the product gains a secondary marketing authorisation or is withdrawn from the market (see Figure 5.3).[8]

The mandatory second approval for *regenerative medicine products* is unique for the conditional approval. While *pharmaceuticals* are re-examined every eight years to confirm safety and efficacy as part of post-marketing requirements, there is no need to demonstrate additional efficacy (see section 5.5).[13]

For standard marketing authorisation procedures for *pharmaceuticals* it is mandatory to adhere to the Common Technical Document standards of the ICH for all new drug submissions in Japan.[14] It is possible for foreign developers of *pharmaceuticals* to collect data outside Japan while building a 'submission dossier', but it is mandatory to collect single dose safety and pharmacokinetics data in a Japanese study group. It is also recommended to include a Japanese study group in a confirmatory study.[15] Given limited experience with the conditional approval scheme so far it is unclear to what extent these regulations are also applicable to *regenerative medicine products.*

5.3.2. Schemes to facilitate early access

Regenerative medicine products can qualify for the regulatory pathway for orphan products. *Regenerative medicine products* that receive orphan designation can be reviewed with priority (PMD Act Article 23-27(7)).[6]

5.3.3. Regulation of incorporated medical devices

Combination products that consist of a *regenerative medicine product* combined with a *pharmaceutical*, and/or *medical device* are always regulated as *regenerative medicine product.* Hence, all provisions for 'clinical research' under the RM Act (see section 5.2.1) and for 'clinical trials' and marketing authorisation procedures under the PMD Act (see section 5.2.2 and section 5.3.1) apply.

5.3.4. Possibility to rely on data other than clinical trials for demonstration of efficacy and safety

Given that the two-phased conditional approval scheme for *regenerative medicine products* has been recently implemented, no clear standard for the evaluation of clinical data has appeared. The regulations stipulate the possibility to rely on observational data for demonstration of safety and probable efficacy in relatively small exploratory studies that use surrogate endpoints and a heterogeneous study population.

5.4. Manufacturing and quality requirements for advanced therapies

Manufacturing and quality requirements differ between *regenerative medicine* that are regulated under the RM Act, and *regenerative medicine products* that are regulated under the PMD Act. In general, requirements under the PMD Act (marketing authorisation) are stricter than under the RM Act (clinical research). The PMDA indicated that the most important differences are the following:

(i) The requirements for manufacturing facilities and equipment are less strict under the RM Act than under the PMD Act.

(ii) Under the RM Act, Process Validation Standard is not as clearly specified.

(iii) Only *regenerative medicine products* regulated under the PMD Act need to comply with the *Minimum Requirements of Biological Ingredients* and the Japanese GMP regulations that are specific for gene-, cell, and tissue-based products (i.e. *Good, gene, Cellular and Tissue-based product manufacturing Practice (GCTP)*).[6]

The PMDA indicated that GCTP are similar to GMP regulations for biologics. However it includes other aspects, such as increased reliance on risk analysis. The Minimum Requirements for Biological Ingredients includes aspects of donor eligibility, testing for adventitious agents and record keeping.

There are specific regulations for cell processing facility standards and manufacturing and quality control under the RM act (RM Act Articles 35-54, RM cabinet ordinance no. 278 Articles 3-6, and RM ministerial ordinance Articles 72-112).[6]

Below we primarily discuss manufacturing and quality requirements for *regenerative medicine products* under the PMD Act. Where relevant we will also discuss aspects of quality and manufacturing requirements under the RM Act (e.g. regulation of cell processing facility licensing).

Manufacturing and quality requirements for advanced therapies under the PMD Act

Japan has several regulations and guidelines in place that are specific for manufacturing and quality requirements for advanced therapies regulated as *regenerative medicine products* under the PMD Act (see Table 5.1). In comparison with international standards to guarantee safety and quality, there are two guidelines that together have a similar scope to the international standards of Good Tissue Practice (GTP): *"General Principles for the Handling and Use of Cells/Tissue-Based Products"* (PFSB/MHLW Notification No. 1314 Appendix 1 – 2000) and *"Standards for Biological Ingredients"* (MHLW Public Notice No. 210 – 2003), which was amended and renamed as *"Minimum Requirements for Biological Ingredients"* (MHLW Public Notice No. 375 – 2014).[16]

Regenerative medicine products also need to comply with *Good, gene, Cellular and Tissue-based product manufacturing Practice* (GCTP) upon authorisation of the product and throughout the post-marketing phase. GCTP requirements are comparable to Good Manufacturing Practice (GMP),[16] with additional unique aspects that are specific for *regenerative medicine products* such as the evaluation of risk profiles and quality control measures that are typical for determining safety of advanced therapies (e.g. tumourigenicity testing).

There are various other guidelines in place for specific quality aspects of *regenerative medicine products* (see Table 5.1). However, these guidelines do not cover all aspects of chemistry, manufacturing and control. When absent, standards for *regenerative medicine products* are determined on a case-by-case basis, based on a risk analysis and product characteristics. Information on specific manufacturing and quality requirements from the relevant regulations and guidelines are described below.

5.4.1. Starting materials

The source and selection of human cells as raw material, including somatic stem cells, induced pluripotent stem cells, and embryonic stem cells, needs to be appropriate for its intended use (*Guidelines on Ensuring Quality and Safety of Products Derived from Processing*; PFSB/MHLW Notification No.0906-2-6).

There are several safety measures in place for human cell starting materials. Both autologous and allogeneic donors are required to be interviewed, screened and tested for eligibility. Donors are required to be tested for infectious agents such as HIV and hepatitis B and C. Other non-infectious diseases are also taken into consideration, such as malignant tumours, metabolic and endocrine disorders, and specific genetic disorders. Furthermore, an informed consent needs to be obtained from donors. In addition, animal materials that serve to prevent contamination with bacteria, fungi, viruses, or prions during cell processing will need to be justified with respect to safety.[16]

5.4.2. Active substances

Active substance often correlates with starting materials and the final product for advanced therapies. Therefore, requirements for active substances are described throughout section 5.4 (section 5.4.1, 5.4.4, 5.4.5).

The PMDA indicated that any substances that are used during processing or that are part of the final process and that are derived from animal or recombinant technology have to adhere to the Minimum Requirements for Biological Ingredients.

5.4.3. Excipients and processing aids

The guideline *Minimum Requirements for Biological Ingredients (MHLW Public Notice No. 375 – 2014*) specifies standards for 'biological materials' (human, animal, and micro-organism originating material, excluding plant material) that are used in manufacturing. The standards in this guideline are outlined for specific product classes (e.g. specific vaccines) and cover both manufacturing control and testing protocols.[17] The guideline also specifies standards for the use of additives and media components (e.g. human serum albumin).[16] Products that do not adhere to the standards in *Minimum Requirements for Biological Ingredients* are not allowed to be sold on the market in Japan (PMD Act Article 65-6).[6] A Japanese association indicated that this is a key aspect for developers to take into consideration when developing a *regenerative medicine product*.

5.4.4. Product characterization

Due to the complexity of *regenerative medicine products* it is difficult to set a standard for product characterization. To deal with this complexity, the Japanese regulators have implemented a new quality and manufacturing standard for *regenerative medicine products*, that was enacted simultaneously with the PMD act in 2014: the "*Good, gene, Cellular and Tissue-based product manufacturing Practice (GCTP)"*.

GCTP mainly focuses on how to design appropriate methods for characterising products, rather than on the specific evaluation criteria that need to be adhered to when applying these methods. For example, the process to purify a product, or the process to determine the differentiation of cells needs to be validated, instead of outcome measures such as the purity of a product or the differentiation results of a cell population.[9] An association indicated that the critical attribute of a *regenerative medicine product* needs to be determined for approval.

5.4.5. Manufacturing

GMP

Manufacturing of *regenerative medicine products* for clinical trials needs to comply with GMP for investigational products,[6] which is less stringent than full GCTP compliance. During development *regenerative medicine products* do not have to comply with all aspects of GMP, because of the on-going development of product quality.[16] Upon marketing authorisation, the product will need to adhere to the Japanese specific *Good, gene, Cellular and Tissue-based product manufacturing Practice (GCTP*).[6] GCTP aims to define quality targets that can be continuously monitored, and to improve cell processing based on risk control and management.

Japan is part of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) of the GMP inspections. However, the GMP type regulations (GCTP) are not fully compliant with the PIC/S requirements.

Licensing / accreditation

Japanese companies that market *regenerative medicine products* are required to obtain a license from the MHLW to manufacture these products, whereas foreign companies need to go through an accreditation procedure by the MHLW.

Both domestic and foreign manufacturers need to comply with GCTP building and facility standards, and adhere to the requirements for human resources in order to obtain a license (PMD Act, Article 23-22, 23-24, 23-25). All manufacturers sites, domestic and foreign, are subject to inspection by the PMDA (PMD Act, Article 23-23).[6]

Manufacturing sites are subject to inspection of the PMDA every two years. The PMD Act also specifies that if there are indications that inspection is needed, or that questions arise from the regular progress of post-marketing measures, the PMDA can inspect manufacturing sites. Recently, the PMDA introduced a specific inspection procedure to enforce compliance with GCTP.[19]

When medical institutions outsource cell processing to another facility for the conduct of clinical research with *regenerative medicine* under the RM Act, these facilities need to hold a license. Japanese facilities need to apply for a license at a MHLW Regional Bureau (RM Act, Article 38). If granted, these licenses are valid for five years (cabinet ordinance for the enforcement of the RM Act, Article 4). Each time a facility applies for a license fees are applicable. Foreign cell processing facilities need to obtain accreditation by the MHLW (RM Act, Article 39).[6]

Licenses are not necessary for cell processing within Japanese medical institutions. However, the MHLW Regional Bureau needs to be notified (RM Act, Article 40).[6] Facility requirements and standards for manufacturing and quality control are defined in RM Act Articles 42, 44.[6] They are the same irrespective of the risk class of the regenerative medicine.[20]

Batch release control

The PMDA indicated that a batch release system is not in place under the PMD Act. Under the PMD Act the sponsor bears responsibility for the manufacturing and control process. Under the RM Act the medical institution or physician is responsible for the quality and manufacturing aspects of clinical research.[6] Manufacturing sites are subject to inspection under the PMD Act but not under the RM Act.

Contamination

Prevention of contamination with bacteria, fungi, and viruses, or abnormal prions originating from biological materials is guaranteed by the quality guidelines in place (Guidelines on Ensuring Quality and Safety of Products Derived from Processing; PFSB/MHLW Notification No.0906-2-6). Quality management systems need to include processes that guarantee control of sterility and contamination with other cells. Eligibility of the selected cells or tissues needs to be supported with specifications of technical capacities how to handle the materials. The substances and instruments used to prevent contamination need to be specified. [16]

Purity, stability and potency

The PMDA indicated that various quality requirements are applicable, which are determined case-by-case. These include identification tests, purity tests, tests to determine process-related impurities, tests for cell-derived undesirable physiologically active substances, sterility tests (including mycoplasma, endotoxin and virus testing), potency tests and other assays to determine cell quantity and cell viability for example.

Traceability

The GCTP guidelines specify that a sponsor should deposit records on donor or raw material of *regenerative medicine products* according to the standards for *Minimum Requirements for Biological Ingredients.* Information for *regenerative medicine products* on human allogeneic source material or excipients need to be kept for 30 years after the product expiration date by sponsors or 20 years by medical institutions. For other source materials than human allogeneic source material, records need to be kept for 10 years after product expirations. Specimens need to be kept for 10 years after product expiry and medical institutions are required to keep patient records for 20 years.[16] A national registry system for *regenerative medicine products* regulated under the PMD Act is in development.[8] The PMDA indicated that the same regulations are in place to ensure traceability under the RM Act.

To ensure traceability along the supply chain during the post-marketing phase, all stakeholders that are involved in distribution need to keep records (PMD Act Article 68-7). All distributors also need to have a license of the local government, comply with building and facility standards, ensure human resource requirements, and adhere to good distribution practice (PMD Act Article 40-5 to 40-7).[6] Both regenerative medicine products that are currently on the market in Japan, JACE and JACC, are subject to these traceability requirements.[21]

5.4.6. Differences in manufacturing and quality requirements between autologous / non-autologous products

Manufacturing and quality requirements for autologous, allogeneic and xenogeneic cells are the same. However, manufacturing and quality requirements differ between the RM Act and the PMD Act as the Minimum Requirements for Biologic Ingredients are not applicable under the RM Act. Instead, manufacturing and quality requirements are described in the RM Act and its ordinances.

5.4.7. Description of processes of approval of changes in manufacturing processes of advanced therapies

Any change in the manufacturing process needs to be reported to the PMDA using a standard variation application. Given the fact that no *regenerative medicine products* have been conditionally approved so far it is not clear how changes in manufacturing after approval will be dealt with. The PMDA indicated that regulations for post-marketing manufacturing changes for *regenerative medicine products* has not been implemented yet.

5.5. Post-marketing requirements for advanced therapies

5.5.1. Comparison of post-marketing requirements of advanced therapies with chemical-based drugs

Basic post-marketing requirements are the same for *regenerative medicine products* and (chemical-based) *pharmaceuticals*. These basic requirements include compliance with Good Post-Marketing Surveillance Practice/Good Post-Marketing Study Practice and Good Vigilance Practice (GVP).[22,23] Both *regenerative medicine products* and *pharmaceuticals* are re-examined several years after the initial approval. Re-examination of post-marketing data is required for all approved *pharmaceuticals* to re-confirm safety and efficacy after a pre-determined period of time, which is typically eight years post-marketing.[13] In addition, sponsors are required to implement a Risk Management Plan in Japan (J-RMP) for *regenerative medicine products* and chemical-based *pharmaceuticals* since 2013. The two pillars of the RMP are a Pharmacovigilance Plan and a Risk Minimizing Action Plan. Basic requirements are safety reporting and providing medical information on the product, respectively.[24]

The Japanese regulations also stipulate several standard post-marketing measures that can be included in the RMP based on the anticipated risk of the product. These measures include early post-marketing phase vigilance, post-marketing observational and clinical studies, post-marketing informed consent, and enhanced information provision to health care professionals.[24] Some of these requirements are mandatory for *regenerative medicine products* (see section 5.5.2), while they are optional for *pharmaceuticals*.

5.5.2. Description of additional post-marketing requirements specific for advanced therapies

Authorisation of *regenerative medicine products* under the conditional approval scheme requires demonstration of quality and safety, plus promising efficacy data (section 5.4). Post-marketing studies subsequently need to confirm safety and efficacy of the product in the post-marketing phase. As no *regenerative medicine product* has been authorized via this pathway so far, it is unclear what the specific study design of these requirements will be. Recently, an investigational *regenerative medicine product* that consists of autologous skeletal myoblast sheets, obtained a recommendation for approval by the PMDA. The sponsor is required to perform a three-year study that will enrol at least 50 patients for long-term follow up.

The often small study groups that are used in initial 'clinical trials' with *regenerative medicine products* increase the risk of missing adverse reactions. The PMD Act therefore mandates to implement specific post-marketing safety and quality measures for *regenerative medicines products*.[7] All patients that are treated with *regenerative medicine products* after conditional approval need to give an informed consent (PMD Act Article 68-4).[6] In addition, marketing authorisation holders need to conduct post-marketing safety and efficacy surveillance (PMD Act Article 68-10, 68-13), plus submit Period Infectious Disease Surveillance Reports to the PMDA (PMD Act Article 68-14, 68-15).[6] A patient registry is recommended to support the conditional approval with post-marketing safety and efficacy data.[9] The PMDA is creating a platform to help health care professionals maintain their records.[8]

If a sponsor fails to demonstrate an anticipated positive benefit-risk profile of a *regenerative medicine product* after the time-limited term of seven years, MHLW can revoke the marketing authorisation.[7] This is different from standard approval procedures because the second validation of clinical benefit, the re-examination of safety and efficacy, is not regulated as strict as for conditionally approved products.

5.5.3. Other relevant aspects of post-marketing requirements for advanced therapies

There are two funds to compensate patients that suffered from adverse events related to the treatment with *regenerative medicine products*. One fund compensates patients in case of any serious adverse events (the Adverse Reaction Relief Fund System), when the product was used appropriately. The second fund compensates patients that suffer from infectious disease that were transmitted by any products that were derived from human or animal material, including *regenerative medicine product* treatment (Relief Fund System).[6]

5.6. Routes for patients to have access to advanced therapies outside of clinical trials and marketing authorisation

The RM Act governs 'clinical research' of *regenerative medicine* that consist of *processed* material for which safety and efficacy have not been established in a formal marketing authorisation process.[1] *Regenerative medicines* are currently non-approved therapies in most cases, because 'clinical research' under the RM Act is intended for academic purposes. However, the PMDA indicated that off-label treatment with *regenerative medicine products* (approved under the PMD Act) is possible under the RM Act. Moreover, even if a *regenerative medicine product* has been approved under the PMD Act, treatment can still occur with a *regenerative medicine* that resembles the branded product under the RM Act. Administration of *regenerative medicines* in clinical research is conducted under the medical supervision of a physician and all legislation and regulation related to the RM Act is applicable. Previous to the new legislation, this process was subject to guidance only.[7]
Access to an investigational *regenerative medicine product* regulated under the PMD Act could be desirable for more patients than can be included in clinical trials. Under these circumstances, patients may obtain access to the investigational *regenerative medicine product* for compassionate use outside of clinical trials. The PMDA indicated that compassionate use for investigational *regenerative medicine products* is possible under the general compassionate use scheme of the PMD Act.

5.7. Views of stakeholders on the regulatory framework

The newly implemented legislations for *regenerative medicines* in Japan provide a specific regulatory pathway for research and marketing authorisation of advanced therapies. A Japanese association indicated that the new legislation is likely to

facilitate the development of new products (PMD Act) and enhance the protection of patients (RM Act). This expectation has also been voiced by interviewed developers. Below we discuss specific factors that facilitate or hinder development of advanced therapies in Japan. Given that the regulatory framework is relatively new and experience with use of the framework is limited, we will in some cases discuss expectations of stakeholders rather than actual experiences.

5.7.1. Factors facilitating development and availability of advanced therapies in Japan

General:

- Overall, an association indicated that many aspects of the new regulatory framework are not yet set-in-stone. Hence, flexibility of regulators in implementing the framework was deemed essential for success;
- An association mentioned that the Japanese government is facilitating the field of regenerative medicine through the Regenerative Promotion Act;
- The Japanese association for regenerative medicine indicated that the RM Act has improved the protection of public health. Before its enactment, regenerative medicines were merely regulated under standard medical care. Under the RM Act, investigators need to collect safety and efficacy data and there are incentives to gain systematic knowledge about the use of regenerative medicine in standard medical care.

Preclinical studies:

- A Japanese developer indicated that the guidelines for preclinical studies are sufficiently clear and specific. Guidelines are in place that describe which preclinical studies are required for specific types of cell-based regenerative medicine products, such as somatic cells, induced pluripotent stem cells and embryonic stem cells.

Clinical trials:

- There is a general expectation among developers that the time to market for regenerative medicine products will substantially decrease with the introduction of the conditional approval scheme. However, given that no product has received authorisation through the scheme so far it is difficult to substantiate this claim. A Japanese developer recently received approval of the PMDA for a product that consists of myoblast sheets, based on safety and feasibility data originating from earlier stage clinical development only (phase I and IIa). Clinical efficacy data remains to be proven in larger clinical trials after conditional marketing authorisation.

Manufacturing and quality:

- A Japanese developer pointed to a well-established network of Japanese institutions in relation to cell processing and product characterization. Several steps are outsourced to other institutions with specialised knowledge on cell processing, which indicates that investigators do not need to rely on their own cell processing capacities only.

5.7.2. Factors hampering development and availability of advanced therapies in Japan

General:

- To date, not many products are being investigated under the PMD Act. The Japanese association for *regenerative medicine* and other developers attributed this observation to a lack of funding. Researchers can start with a small grant for clinical research under the RM Act, but this may be insufficient to enter the more expensive clinical trials under the PMD Act. Clinical trials were especially deemed expensive due to the need for mandatory compliance with manufacturing and quality requirements in order to obtain marketing authorisation (GCTP). In addition, a Japanese developer indicated that his university does not have sufficient resources to conduct large phase III clinical trials that are required after conditional approval. Instead, large phase III studies are most likely to be performed by a company (see section 5.7.2);
- A Japanese developer indicated that the RM Act increased the standards for clinical research and not all investigators in Japan deemed this necessary.

Specific hampering factors that were mentioned were:

Manufacturing and quality:

- Compliance with the regulation *Minimum Requirements for Biological Ingredients* with respect to the choice of biological ingredients was described as most challenging in manufacturing and quality standards that are in place for *regenerative medicine products*. There is no harmonization in biologic material regulation, which means that foreign developers cannot change their biological material if needed once they have established product characteristics to large extend and seek marketing approval in Japan;
- Compliance with GCTP was indicated to be very expensive by a Japanese developer. There is a lot of testing required, including testing of all biologic materials that are used during cell processing, including animal derived products and active substances. All materials need to be checked in the final product and evidence of suitability of these materials has to be in place. These strict regulations are not applicable under the RM Act and therefore many investigators express preference for clinical research under the RM act rather than going for clinical trials under the PM act.

Post-marketing requirements:

- Post-marketing surveillance by performing observational studies remains to be organised for *regenerative medicine products*. This is a new role for the PMDA, in which they have limited experience. The Japanese society for regenerative medicine indicated that success of the new PMD Act will depend on the collection of data in the post-marketing phase after conditional approval in order to protect safety and to facilitate the approval of new *regenerative medicine products*. The development of strategies and methodologies for observational studies were believed to be critical to collect such data.

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6. Analysis of the regulatory framework governing advanced therapies in South Korea

6.1. Overview of regulatory framework for advanced therapies in South Korea

6.1.1. Regulatory responsibilities and mandate

The Ministry of Food and Drug Safety (MFDS), which was formally known as the Korean Food and Drug Administration, is the regulatory agency for food, *drugs, biologic products, medical devices* and cosmetics in South Korea.[1] There are three separate sectors of the MFDS; headquarters, the National Institute of Food and Drug Safety (NIFDS) and six Regional Offices.

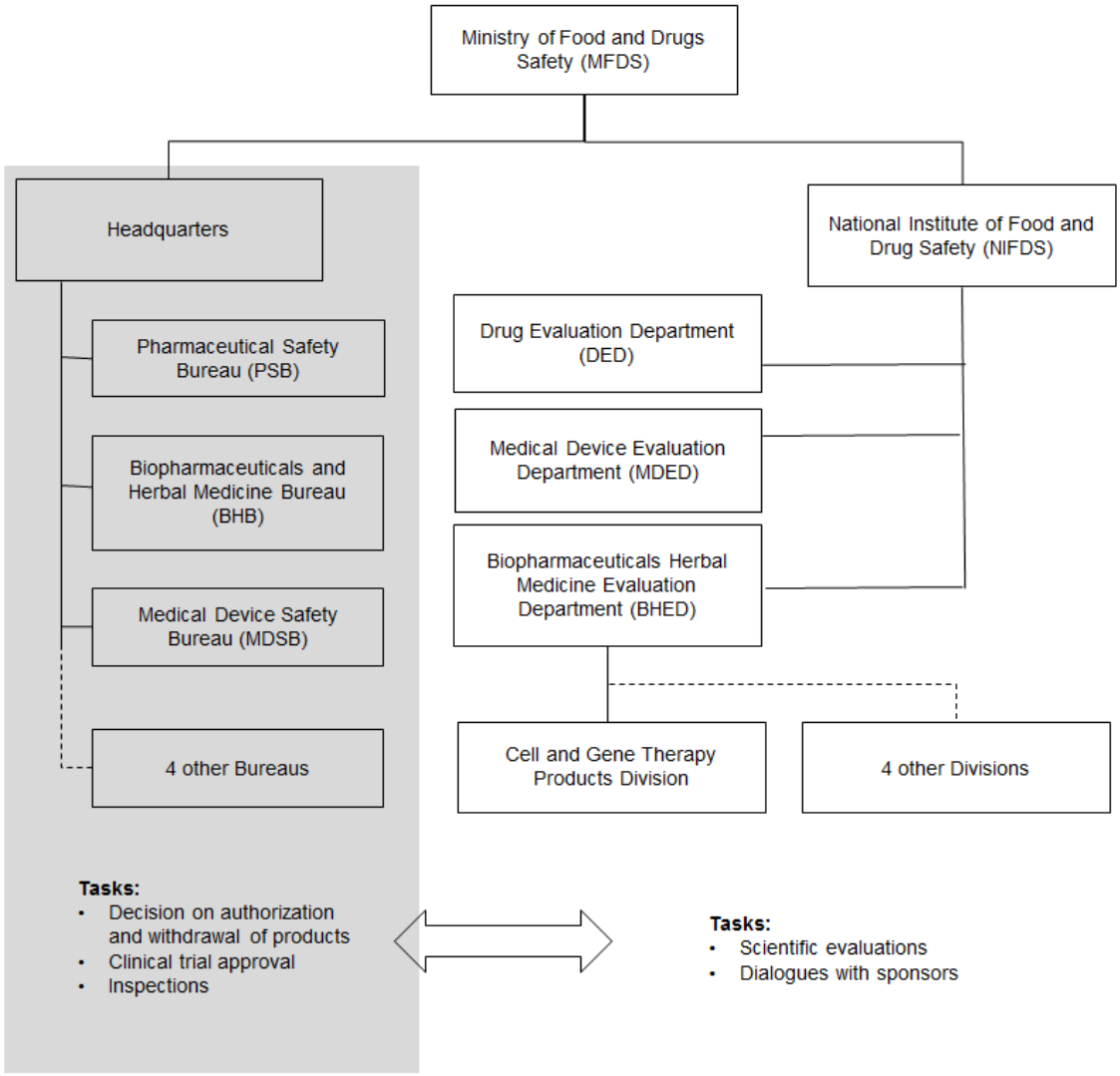
Within the headquarters of MFDS, bureaus are responsible for *drugs* (Pharmaceutical Safety Bureau - PSB), *biologic products* (Biopharmaceutical and Herbal Medicine Bureau - BHB), and *medical devices* (Medical Device Safety Bureau), among others.[1,2] Responsibilities include clinical trial approval (PSB, see section 6.2), marketing authorisation (see section 6.3) and post-marketing surveillance (see section 6.5).

Within the NIFDS, departments are responsible for evaluation of quality, safety, and efficacy data that are part of submissions for Investigation New Drugs (see section 6.2) and New Drug Applications for *drugs* (Drug Evaluation Department) and *biologic products* (Biopharmaceuticals and Herbal Medicine Evaluation Department) (see section 6.3);[1]. Responsibilities also include evaluation of submissions for clinical trial authorisation (see section 6.2) and Korea License Holder applications (see section 6.3)[3] of *medical devices* (Medical Device Evaluation Department). The departments within NIFDS are supported by separate divisions that oversee evaluation of product categories within the general class of *drugs* and *biologic products*.[2]

Within the Biopharmaceuticals and Herbal Medicine Evaluation Department (BHED), there are separate divisions for *biologic products*, recombinant protein products, *and cell and gene therapy products*. Figure 6.1 provides an overview of the MFDS bureaus and departments that are involved in the regulation of medical products, including advanced therapies. Advanced therapies are primarily regulated as *biologic product* by the BHB and evaluated and authorized by the cell and gene therapy division of the BHED.[1]

The six Regional Offices are responsible for on-site inspections, implementation of policies and managing marketed products in their region.[4]

Figure 6.1 Overview of MFDS bureaus and departments involved in the regulation of medicinal products



6.1.2. Description of regulatory framework

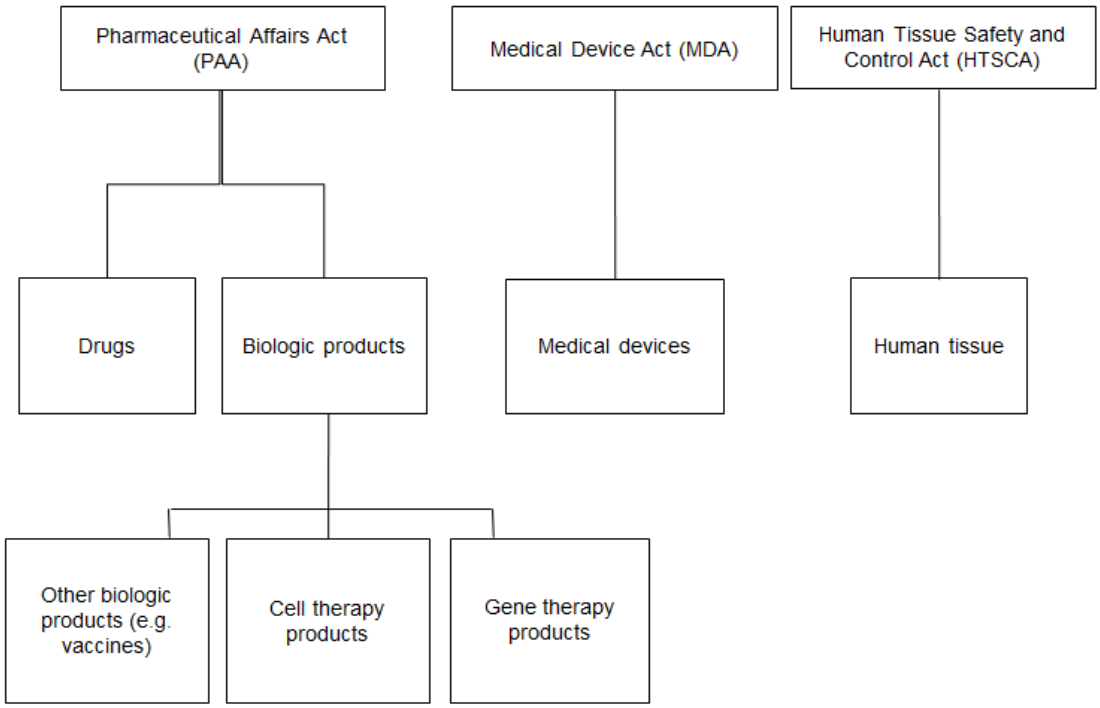
The South Korean regulatory framework consists of a three-tiered system of acts, regulations and guidance. Acts define the scope of regulation. Regulations comprise Enforcement Rules and various MFDS Notifications that prescribe detailed procedures for review, approval, and management of medicinal products, including advanced therapies. The MFDS has also developed various guidelines that provide non-binding guidance to MFDS staff and the industry.[4]

Drugs and *biologic products* are regulated under the Pharmaceutical Affairs Act (PAA),[5] while *medical devices* are regulated under the Medical Device Act (MDA).[6] The PAA is enforced by the *Enforcement rule of Medicinal Product Safety*. Approximately 30 MFDS Notifications are issued under the PAA of which The *Regulation on Review and Authorisation of Biological Products* (RRABP) and *Regulation on Investigational New Drug Application for Medicinal Products* are of primary importance for marketing authorisation of advanced therapies (see section 6.1.3).

Specific guidelines that are applicable to advanced therapies include *the Guideline on Replication Competent Virus Test for Gene Therapy Products* and the *Guideline on Manufacture and Quality Control of Cell Therapy Products*.[4] The MFDS may also refer to or use guidelines for advanced therapies from the US or Europe. However, determination of the ultimate applicable standards is at the discretion of expert committees (see section 6.2 and 6.3). Furthermore, ethical conduct with human stem cells, in particular embryonic stem cells, is regulated under the Bioethics and Safety Act.[7]

Figure 6.2 provides a schematic overview of the regulatory framework in South Korea under which advanced therapies and other medicinal products are regulated.

Figure 6.2 Overview of regulatory framework for medical products, including advanced therapies, in South Korea



The legal documents that are relevant for the regulation of advanced therapies under the PAA and MDA are published by the Korean government in Korean only. Therefore, the references in this document do not specifically refer to these original documents, but to secondary sources that cite and/or quote the original documents. An overview of regulations and guidelines is provided in Table 6.1. References to acts are unofficial translations of the original acts. The MFDS has been criticized for not having available English versions of its regulations available.[8] In general, there is limited public knowledge on the regulatory framework and approval decision making processes for advanced therapies in South Korea.[9,10]

Table 6.1 Main regulations, and guidelines that are applicable to cell therapy products and gene therapy products [only available in Korean]. Adapted from Choi et al. 2015[4] and Lim[11]

Product type	Document
Regulation	
All medicinal products, including advanced therapies	Enforcement Rule of Medicinal Products Safety Regulation on Approval of Investigational New Drug Application for Medicinal Products Regulation on Pre-review of Application Documents for Medicinal Products Regulation on Designation of Orphan Drugs Regulation on Re-examination of Medicinal Products Regulation on Re-evaluation of Medicinal Products
Biologic products, including advanced therapies	Regulation on Review and Authorisation of Biological Products
Guidelines	
Biologic products, including advanced therapies	Guideline on Adventitious Virus Test for Biological Products for Human Use Guideline on the Requirements for Quality of Biologics in Clinical Trials Guideline on Process Validation of Biological Products
Cell therapy products	Guideline on Manufacture and Quality Control of Cell Therapy Products Guideline on Mycoplasma Test Suitable for Cell Therapy Products Guideline on Potency Testing of Cell Therapy Products Guideline on Stem Cell Products (draft) Guideline on the Nomenclature of Cell Therapy Products Guideline on Tumourigenicity Study of Stem Cell Products (draft) Guideline on GMP for Cell Therapy Products
Gene therapy products	Guideline on Replication Competent Virus Test for Gene Therapy Products
Cell therapy products & Gene therapy products	Guidelines on Cell Therapy and Gene Therapy Products

6.1.3. Regulatory framework for advanced therapies

Advanced therapies as defined in this report are classified as a *biologic product*, with the exception of minimally manipulated cell therapies intended for non-homologous use that are produced by medical institutions. In addition, the definition of *cell therapy product* is also broader for other subtypes (see section 6.1.4). Developers have to follow marketing authorisation procedures with advanced therapies classified as *biologic products* (see section 6.3). All legal definitions of regulated medicinal products and definitions originating from guidelines can be found in Table 6.2.

Table 6.2 Product definitions

Product type	Definition
Drugs (PAA, Article 2)	Product falling under any of the following subparagraphs: (a) Those, other than quasi-drugs, among products listed in the Korean Pharmacopoeia; (b) Products used for the purposes of diagnosis, medical care, alleviation, treatment or prevention of diseases of human beings or animals, excluding appliances, machinery and equipment; (c) Products, other than appliances, machinery or equipment, used for the purpose of exerting pharmacological effects upon the structure or functions of human beings or animals.
Cell therapy product (RRABP, Article 2)	A medicinal product manufactured through physical, chemical, and/or biological manipulation, such as in vitro culture of autologous, allogeneic, or xenogeneic cells. However, this definition does not apply to a case where a medical doctor performs minimal manipulation (e.g. simple separation, washing, freezing, thawing, and other manipulations, while maintaining biologic properties) that does not cause safety problems of the cells in the course of surgical operation or treatment at a medical centre.
Gene therapy product (RRABP, Article 2)	A genetic material or a medicinal product containing such genetic material intended to be administered to human beings for treatment of disease.
Medical device (MDA, Article 2)	Any instrument, machine, contrivance, material or similar article that is used on human beings or animals either alone or in combination with other devices and that falls under any of the following Items provided below. However, drugs or quasi-drugs under the Pharmaceutical Affairs Act or, among the disabled-assistive-devices under Article 65 of the Act for Welfare of the Disabled, artificial limbs and orthotics shall be excluded. <Amended on April 11, 2007> 1. Articles used for the purpose of diagnosis, cure, alleviation, treatment, or prevention of illness; 2. Articles used for the purpose of diagnosis, cure or alleviation of or compensation for an injury or disability; 3. Articles used for the purpose of test, replacement, or modification of the structure or functions [of the body]; or 4. Articles used for the purpose of control of conception.
Human tissue (HTSCA, Article 3)	(a) Bones, joints, myofascia, skin, amnion, ligament, and tendon; (b) Heart valves and veins; (c) Body parts which may be recovered and transplanted for a person's health, physical recovery and prevention of disability, and which may be determined by Presidential Decree.

The Korean regulatory framework specifically mentions *cell and gene therapy products* in the MFDS notification *Regulation on Review and Authorisation of Biological Products* (RRABP). In this document these products are categorized as *biologic products* regulated under the PAA and RRABP. The definitions for *cell and gene therapy products* can be found in the RRABP. *Gene therapy product* is defined as:[4]

- *"A genetic material or a medicinal product containing such genetic material intended to be administered to human beings for treatment of disease."* (RRABP, Article 2)

It is further specified that *gene therapy products* include genetically engineered ex-vivo *gene therapy products* and vectors produced by recombinant technology, such as plasmids, vectors, bacteria, cells, and siRNAs. A few product types are excluded from the definition of *gene therapy product*. More specifically, products that are not derived from recombinant technology, such as chemically produced nucleic acids and wild-type viruses are not considered *gene therapy products*.[4] These fall outside of the definition of advanced therapy. However, although these products are not considered *gene therapy products* they are nonetheless regulated as *biologic products* under the PAA.

Hence, there are no consequences for the applicable regulation for marketing authorisation, although other standards for quality and manufacturing as defined in guidelines may apply.

Cell therapy product is defined as:[4]

- "*A medicinal product manufactured through physical, chemical, and/or biological manipulation, such as in vitro culture of autologous, allogeneic, or xenogeneic cells. However, this definition does not apply to a case where a medical doctor performs minimal manipulation (e.g. simple separation, washing, freezing, thawing, and other manipulations, while maintaining biologic properties) that does not cause safety problems of the cells in the course of surgical operation or treatment at a medical centre."* (RRABP, Article 2)

6.1.4. Products exempted from requirements to obtain marketing authorisation

Cell therapy products are considered a *biologic product* regardless of source material origin (e.g. autologous vs. allogeneic), and intended use (e.g. homologous use). Thus, *cell therapy products* are categorized as *biologic product* firstly on the basis of more-than-minimal manipulation and cover most types of advanced therapies. Secondly, the definition of *cell therapy products* also includes minimally manipulated cells that are produced outside of medical institutions (e.g. by companies), regardless of intended use. Therefore, the definition of cell therapy product does not fully correspond to the definition of advanced therapies, it is narrower from one perspective and broader from another. On one hand, minimally manipulated cell therapies that are intended for non-homologous use that are produced within medical institutions are not regulated as *cell therapy product* and no marketing authorisation is required. On the other hand, minimally manipulated cell therapies that are for homologous use that are produced by industry fall within the scope of *cell therapy product* and require marketing authorisation.

Since the inclusion of *cell therapy products* in the RRABP in 2001, any cell therapies that were in use before 2001 have been conditionally approved (see section 6.5.2) under the PAA to ensure the conduct of post-marketing clinical studies. These included autologous cell therapies for severe burns are cartilage repair.[4]

In summary, the following product types are excluded from the definition of *cell therapy products and* are not regulated as *biologic products*:

(1) cell therapies that have been minimally manipulated within medical institutions that do not cause safety concerns for surgical procedures or standard medical care.[4] These products are regulated under the Medical Service Act;[11]

(2) *Human tissue* intended for transplantation is regulated under the Human Tissue Safety and Control Act (HTSCA).[12]

6.1.5. Description of methods to control advanced therapies without therapeutic indication

Information indicating the regulations for commercialisation of cell-based cosmetic products are unavailable.

6.2. Framework governing clinical trials with advanced therapies

6.2.1. Responsible parties and tasks for clinical trial authorisation and supervision

Investigational use of *drugs*, *biologic products*, and *medical devices* is regulated by the MFDS. Clinical trials need to be conducted according to Good Clinical Practice (GCP) and clinical trials on *biologic products* need to be authorized based on an Investigational New Drug (IND) submission.[4] All clinical trials have to be authorized by the PSB at MFDS after evaluation of the IND submission by the appropriate evaluation department.[1]

Clinical trial authorisation of advanced therapies

Sponsors of advanced therapies need to apply for an IND. Within the MFDS, the BHB is responsible for enforcement of Good Clinical Practice (GCP) by conducting inspections, and the cell and gene therapy products division of the BHED evaluates IND submissions for *cell therapy products* and *gene therapy products*.[4] The standard review time for an IND is 30 days. Once clinical trials are approved they must be conducted at a medical institution that has been designated as a clinical trial institution by the MFDS (see Figure 6.1).[4]

Sponsors can submit a pre-review IND to receive regulatory advice on the application documents before official submission.[11] Pre-review of submission dossiers is regulated under *Regulation on Pre-review of Application Documents for Medicinal Products*. The MFDS may seek scientific and ethical advice from the Central Pharmaceutical Affairs Advisory Committee (CPAC) as part of the review of a full *biologic product* IND application. The CPAC is an independent committee of expert from five fields; physicians, pharmacists, professors, statisticians, and lawyers. In addition, consumer representatives are also part of the CPAC.[4] A developer confirmed that this expert panel was involved in the evaluation of their developed product.

The specific requirements for the IND process for all drugs, including all *biologic products* and the sub-categories of *gene therapy products* and *cell therapy products*, are outlined the MFDS Notification *Regulation on Approval of Investigational New Drug Application for Medicinal Products*. In summary, an IND application needs to contain information on manufacturing standards (Good Manufacturing Practice-GMP), quality of the product, safety and efficacy data, plus the clinical protocol. INDs need to be filed before the start of each new clinical trial phase.[4] More detail on the substance of an IND applications is described below.

Investigational products have to formally comply with GMP throughout clinical trials (see section 6.4).[4] While there is no explicit policy that compliance becomes stricter throughout development, it is understood that the MFDS applies flexibility. A developer indicated that CMC requirements for *cell therapy products* and *gene therapy products* differ substantially from *biologic product* requirements. For stem *cell therapy products*, tumourigenicity has to be determined in *in-vitro* and *in-vivo* studies. Carcinogenicity studies only have to be considered for those *cell therapy products* and *gene therapy products* that stimulate growth factors.[4] Specific guidelines for quality studies with *cell therapy products* and *gene therapy products* are published by the MFDS (see Table 6.1).

Preclinical toxicology studies need to be performed in licensed GLP-facilities in Korea.[4] In order to determine the exact preclinical requirements to determine safety and efficacy, such as determining the appropriate animal models and specific assays to determine tumourigenicity, the MFDS uses a flexible, science-based approach to be

able to adapt requirements to specific product characteristics.[1] Preclinical studies have to indicate dose, schedule, route of administration, and the dosage form, if possible depending on the specific product characteristics. The route of administration and the target site should be the same in the animal studies as in the clinical protocol. However, this may not always be possible due to a lack of a suitable animal model and immunogenicity.[1] Furthermore, biodistribution studies are typically required for *cell therapy products* and *gene therapy products*. These can complement toxicology and pharmacology studies.

Clinical protocols to study *cell therapy products* and *gene therapy products* impose additional challenges compared to other *biologic products*. Therefore, for clinical trial design, the MFDS operates in a flexible manner that is science-based and requirements are determined on a case-by-case basis.[1] This approach was also mentioned by a developer who indicated that exact standards for preclinical studies, clinical trial design, enrolment of patients, and follow up is determined in consultation with the MFDS.

If a trial is initiated by an investigator (IIT), the same requirements are in place as for trials that are initiated by sponsors. However, if the investigator can demonstrate that there are no safety concerns for an IIT with *cell therapy products*, and the trial is being conducted for academic research purposes only, the requirements for an IND of an IIT become less stringent. A clinical protocol, approval of the Institutional Review Board (IRB), and informed consent that has been developed by at least five experts in the field will suffice in this case.[4] Results from the IITs may be used for phase I clinical trials that are part of a marketing authorisation procedure, but this only applies to autologous *cell therapy products*.[11]

6.2.2. Comparison of responsible parties with chemical-based medicines

The responsible regulatory bodies for GCP inspections of clinical trials in which chemical-based *drugs* are being investigated is the Pharmaceutical Safety Bureau at headquarters. The Drug Evaluation Department of the NIFDS evaluated IND submissions of chemical-based *drugs* in order to authorize clinical trials.[1,2]

The BHB is the responsible regulatory bodies for GCP inspections of clinical trials in which *biologic products*, including *cell therapy products* and *gene therapy products*, are being investigated. The cell and gene therapy division of the BHED evaluated IND submissions of *cell therapy products* and *gene therapy products* in order to authorize clinical trials.[1,2]

6.3. Framework governing commercialisation of advanced therapies

6.3.1. Approval of advanced therapies

Sponsors need to submit a NDA for *cell therapy products* and *gene therapy products* under the authority of the cell and gene therapy division of the BHED.[1] NDAs for *cell therapy products* and *gene therapy products* need to comply with standard approval procedures for *biologic products*, but guidance is provided how to comply with the standards for b*iologic products* as not all requirements will be applicable or suitable for *cell therapy products* and *gene therapy products*. Relevant general information for *biologic products* and specific information on *cell therapy products* and *gene therapy products* is provided in this section when available.

Review and authorisation of all *biologic products* including advanced therapies is regulated under the RRABP.[4] In order to obtain marketing approval the NDA should contain data about chemistry, manufacturing, and control (CMC) data that is GMP-compliant, preclinical study data that is GLP-compliant, and clinical study data that is GCP-compliant, has to indicate quality, safety, and efficacy of the *biologic product*.[1] For the standard approval procedure for biologic products, phase I to phase III clinical trial results are required.[4] The standard review period for all NDAs is 115 days, including for *cell therapy products* and *gene therapy products*. The MFDS may seek advice from the CPAC during the review of a NDA.[4]

Specific requirements have been developed for *cell therapy products* and *gene therapy products. Annex 2: Types of Information Required for Cell Therapy Products* specifies required safety and efficacy data for authorisation of *cell therapy products; Annex 3: Types of Information Required for Cell Therapy Products* specifies required safety and efficacy data for authorisation of *gene therapy products* (RRABP, Article 25). RRABP Article 30 specifies the requirements for quality for *cell therapy products: Review Criteria for Cell Therapy Products*, and RRABP Article 31 specifies the requirements for quality for *gene therapy products: Review Criteria for Gene Therapy Products.* If the relevant regulations or guidelines are not in place for a particular product, the MFDS may refer to regulations and guidance of other jurisdictions.[4]

The MFDS uses a flexible approach in the evaluation of *cell therapy products* and *gene therapy products.* A flexible approach is needed to handle the challenges that *cell therapy products* and *gene therapy products* impose while regulating these according to the standards of the regulatory framework for *biologic products*. The approach is determined on a case-by-case basis in order to appropriately review risk-benefit profiles of advanced therapies.[1,11]

For *gene therapy products*, the Korean regulatory framework stresses biosafety as an essential component in the development of these products. Biosafety has to be established upon approval because of the potential threat for the health of the patient due to insertional mutagenesis and treatment with replicating viruses, plus the threat for public health due to the potential spread of genetically modified microorganism through shedding or manufacturing procedures. For *cell therapy products*, evaluation of clinical trial results imposes challenges due to the clinical study design. Study groups are often small because of rare or serious conditions and it is not always possible to have a placebo-controlled trial design because of invasive delivery procedures. Adverse events may not be detected in a small patient group for the relatively short duration of the clinical trial, which calls for long-term follow up of patients.[4]

In addition, several alternative regulatory pathways have been adapted to facilitate access to innovative treatment when standard treatment is not available or fails. These alternative pathways include conditional approval of NDAs (see section 6.3.2), pre-review of application dossiers for IND and NDA applications (see section 6.2.1).[4]

6.3.2. Schemes to facilitate early access

Investigational oncology products including advanced therapies may be conditionally approved based on surrogate endpoints, if the clinical trial design is similar to a clinical trial design with clinical endpoints. Consequently, confirmatory clinical data need to be collected in the post-marketing phase.[4]

6.3.3. Regulation of incorporated medical devices

Combination products that consist of cells or tissue and a device, are regulated as a *biologic drug* under the PAA and/or as *a medical device* under the MDA, depending on product specific characteristics.[1,4,11] Thus, combination products are regulated according to the corresponding marketing authorisation processes under the PAA and/or MDA (see section 6.3.1).

6.3.4. Possibility to rely on data other than clinical trials for demonstration of efficacy and safety

The standard procedure for a NDA approval requires clinical trial data from phases I-III in South Korea.[4] There have been discussions to lower the requirements for approval for cell therapy products to clinical data of only phase I studies to indicate clinical safety.[10] This has not been implemented though. Information, including safety and efficacy data and follow-up safety data, that is collected from expanded access (see section 6.6) should be submitted to the MFDS.[4] More specific information on whether and how this data can support NDA submissions is not available.

6.4. Manufacturing and quality requirements for advanced therapies

Upon initiation of clinical trials, sponsors of all investigational *biologic products* have to comply with Good Manufacturing Practice (GMP). To provide guidance on specific requirements for *cell therapy products*, MFDS published the *Guideline on Manufacture and Quality Control of Cell Therapy Products*. In case specific guidance is not available within the Korean framework, the MFDS encourages industry to use guidelines from the US and the EU for manufacturing and quality requirements *for biologic products*, including *cell therapy products* and *gene therapy products*.

The MFDS takes a case-by-case approach when evaluating manufacturing and quality requirements for clinical trials and authorisation of *cell therapy products* and *gene therapy products*. Specific challenges that are taking into account are issues related to biologic activity such as proliferation, migration, and paracrine effects on target tissue.[4]

In the following sections the manufacturing and quality requirements for biologic products, *gene therapy products* and *cell therapy products* are provided.

6.4.1. Starting materials

Donor screening and testing requirements are in place for cell therapy products and gene therapy products.[13] More specific information is not available.

6.4.2. Active substances

It is recommended that any reagents or pharmaceutical components that are used in the manufacturing of cell therapy products and gene therapy products are manufactured under GMP conditions. If they were not manufactured under GMP conditions, quality testing protocols with specifications have to be developed to control quality of these reagents.[4]

6.4.3. Excipients

It is required that any excipients that were used during cell processing are safe and suitable for use as *cell therapy products* and *gene therapy products*. Excipients need to be controlled for contamination with pathogens, because these are typically of biological origin (e.g. human serum albumin).[4]

6.4.4. Processing aids

It is required that any processing aids that were used during cell processing are safe and suitable for use as *cell therapy products* and *gene therapy products*. Processing aids need to be controlled for contamination with pathogens, because these are typically of biological origin (e.g. growth factors).[4]

6.4.5. Product characterization

Product characterization consists of quality testing that includes assays for identity, purity, potency, and viability.[1] A developer indicated that standards of product characterization resemble that of the US the most. Due to the variability between different types of *cell therapy products* and different types of *gene therapy products*, plus the variability in product characteristics in-vivo and in-vitro, a combination of various product characterization assays may be performed to determine cell surface markers, gene expression, protein expression, release of signalling molecules, and other product characteristics to determine specifications that suit the intended clinical use.[1]

A Korean developer indicated that standards for product characterization, in particular potency requirements, become more stringent as product development of cell therapy products progresses. Comparability studies may be required for *cell therapy products* to indicate product characterization and possible changes in CMC data between early and late clinical trials and after marketing authorisation.

6.4.6. Manufacturing

GMP

Before approval of *cell therapy products* and *gene therapy products* NDAs, manufacturers have to comply with GMP. Pre-inspections at manufacturing sites may occur before marketing authorisation procedures and lot release on the market. However, this is not a standard procedure.[4]

Batch release control

Batch control to ensure compliance with the specifications in the license is required before release of a batch after marketing authorisation. Specific lot release requirements are in place for *cell therapy products* and *gene therapy products*. A developer indicated that these differ from most of the standards that are in place for *biologic products*.

To overcome issues with lot release testing for autologous *cell therapy products*, it is possible to include strict in-process testing results in the specifications of the lot release testing of autologous *cell therapy products*.[4]

Contamination

Sterility testing is required for marketing authorisation.[11] Contamination with infectious agents is of concern for *cell therapy product* and *gene therapy products* due to their biological nature. They are not heat-stable and source material may be infected with wild-type pathogens. To ensure sterility, the *Guideline on Manufacture and Quality Control of Cell Therapy Products* includes recommendations to manufacture under aseptic conditions. Moreover, strict microbiologic control is required during cell processing.[4]

The MFDS also provides specific guidance as to how to test contamination of *cell therapy products* with mycoplasma in the *Guideline on Mycoplasma Test Suitable for Cell Therapy Products*, and how to test biologic products for contamination with adventitious viruses in the *Guideline on Adventitious Virus Test for Biological Products for Human Use*. Furthermore, in the *Guideline for Replication Competent Virus Test for Gene Therapy Products* guidance is provided on how to test vectors for possible contamination of viruses that can replicate.[4]

Purity

Purity is a mandatory quality control for final product of *cell therapy products* to ensure that any undesirable impurities originating from raw materials or from cell processing are eliminated upon release of the product.

Stability

Testing to determine the stability of active components of *gene therapy products*, such as the vector or cell, is required.[4,11] There is no information available with regard to *cell therapy products*.

Potency

Multiple assays and measures need to be established for *cell therapy products* to indicate surrogate points for potency, given that the mechanism of action of *cell therapy products* often relies on various factors. Combined, these potency assays need to correlate with clinical outcomes.[1,4] Potency needs to be considered from the moment that clinical trials are initiated, and it is recommended to design the clinical trial in such a way that the outcomes can be linked to potency.[4]

6.4.7. Differences in manufacturing and quality requirements between autologous / non-autologous products

All manufacturing and quality requirements described in this section apply to *cell therapy products* that have been more-than-minimally manipulated, including autologous *cell therapy products.*

6.5. Post-marketing requirements for advanced therapies

6.5.1. Post-marketing requirements of advanced therapies vs. chemical-based medicines

Under the standard approval procedure for *biologic products*, there are several post-marketing requirements and measures in place. These include re-examination and re-evaluation procedures, submission of periodic safety update reports (PSURs), Risk Management Plans (RMPs), product license renewal, GMP inspections, and advertisement monitoring.[1,4] More detail on RMPs, re-examination and re-evaluation is provided below.

RMPs are regulated under the *Enforcement Rule of Medicinal Products Safety*. RMPs need to be in place for all medicinal products including advanced therapies. The RMP needs to contain a strategy to manage product safety, including long-term follow up of clinical studies in order to detect delayed adverse events.

Re-examination and re-evaluation are regulated under the *Regulation on Re-examination of Medicinal Products*, and the *Regulation on Re-evaluation of Medicinal Products*. These regulations are in place for all medicinal products regulated under the PAA, including chemical-based *drugs*, *biologic products*, and *cell therapy products* and *gene therapy products.*[4] Plans for re-examination need to be submitted after

marketing authorisation to ensure post-marketing surveillance of adverse events under normal treatment conditions for a period of time. The requirements for re-examination of *cell therapy products* differ between cell therapy products and drugs as confirmed by a Korean developer. For drugs 3,000 patients need to be followed over a period of six years, whereas for *cell therapy products* 600 patients need to be followed over a period of six years.[4] Labels are updated based on post-marketing safety information. During re-examination of medicinal products, data exclusivity is guaranteed.[4]

Similar to re-examination, re-evaluation procedures are in place for all medicinal products regulated under the PAA. Re-evaluation is a process to update safety and efficacy information, compared to other new treatments and new published scientific evidence, if applicable and available. Upon completion of the re-examination period, re-evaluation needs to occur every five years in order to update the product marketing license.[4] If the sponsor fails to submit updated safety and efficacy data after five years, or if there are safety concerns, the license is not renewed by the MFDS.[1]

6.5.2. Description of post-marketing requirements specific for advanced therapies

There are no standardized regulations for post-marketing requirement for advanced therapies, besides the unique re-examination requirements for *cell therapy products* which require follow-up of 600 instead of 3,000 patients in six years (see section 6.5.1). However, RMPs for *cell therapy products* and *gene therapy products* can contain specific measures to manage safety during the post-marketing phase, such as long-term post-marketing clinical studies for *gene therapy products* that have possible delayed adverse events due to insertional mutagenicity.[4]

Post-marketing requirements to be included in the RMP are determined on a case-by-case basis. Note that cell therapies that were used in standard medical care, prior to the inclusion of these therapy group in the RRABP as *cell therapy products*, were conditionally approved in 2001.[4] After conditional approval, these have been subsequently approved if post-marketing requirements were met (see Annex 6).

The MFDS is piloting a system in which all patients that receive treatment with *cell therapy products* are followed and investigated for the first two years after marketing authorisation.[11] This system includes off-label use of *cell therapy products*. Moreover, a Korean association for advanced therapies indicated that more specific guidance on post-marketing requirements for advanced therapies are in development in South Korea.

6.6. Routes for patients to have access to advanced therapies outside of clinical trials and marketing authorisation

Expanded access to investigational products may be granted for all medicinal products that are regulated under the PAA, including *cell therapy products* and *gene therapy products*. Expanded access can be granted in emergency situations, or for treatment outside of clinical trials.[4]

If clinical trials show promising efficacy results for a serious disease or condition, physicians can apply for expanded access for patients that are not enrolled in those clinical trials by submitting the treatment protocol to the MFDS. After the MFDS approves the treatment protocol, patients can receive investigational treatment outside of clinical trials if approval of the IRB has been obtained and informed consent has been provided by the patient.[4]

Expanded access to investigational treatment can also be provided in emergency situations. These situations need to be evaluated by a physician as 1) serious or life-threatening, in which 2) alternative treatment is unavailable, and 3) that the anticipated clinical benefit can only be reached within a certain time frame. To apply for expanded access in emergency situations, an informed consent and intended supply the product by the manufacturer need to be submitted to the MFDS. If the request is granted, relevant information on adverse events, efficacy, and long-term safety has to be provided to the MFDS.[4]

There are no other means than mentioned in this section by which patients can have access to advanced therapies outside of clinical trials or a marketing authorisation.

6.7. Views of stakeholders on the regulatory framework

The quickly progressing research field in South Korea was described as imposing challenges for regulatory agencies and the regulatory framework itself. The regulatory framework does not seem to be fully adapted to the evolving research field. As a consequence, standards tend to be approached on a product basis and are constantly evolving. Uncertainties about the exact requirements are therefore persistent. A Korean developer indicated for instance that many aspects of the regulatory framework for biological products cannot be directly applied to cell therapy products. There was also an expectation voiced about changes to the regulatory framework in the near future, in particular in line with the new legislation for regenerative medicine in Japan.

6.7.1. Factors facilitating development and availability of advanced therapies in South Korea

General:

- For a relatively long time, the Korean government has stimulated the development of advanced therapies by providing funds for public-private partnerships. The unique aspects of these partnerships was that an industry partner is mandatory for an academic partner to engage, and milestones in the project are directly related to regulatory aspects such as filing an IND;
- In response to the numerous public-private partnerships that were initiated from government funds, the MFDS increased its own capacity to provide sufficient and adequate regulatory guidance to the industry;
- Next to regulatory efforts there are also other government efforts to stimulate development of *cell therapy products* include the establishment of associations that aim to accelerate commercialisation such as GRASC.

6.7.2. Factors hampering development and availability of advanced therapies in South Korea

General:

- A Korean developer described that it was difficult to market a cell therapy product, because of the lack of clear standards. Obtaining a marketing authorisation required a lot of communication between the developer and the MFDS.

6.8. References

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7. Overview of research activities and availability of advanced therapies

7.1. Introduction

The overview of research activities and availability of advanced therapies includes:

- Advanced therapies that have been authorised for commercialisation in each jurisdiction. Per product we collected information about the type of product, the brand name, availability, submission date, approval date, features approval procedure, therapeutic indication, cell-based (yes/no), medical device included (yes/no), reimbursement status, developer, type of organisation, manpower of the organisation and annual turnover (presented in Annex 6);
- Authorised clinical trials of advanced therapies in each jurisdiction (presented in Annex 7). The full references of the publications included in the study are provided in Annex 8;
- The developers involved in on-going research projects and/or involved in advanced therapies that are already available including their size and analysis of the relative weight of academia and non-for-profit sector (presented in Annex 6 and 7).

In the Tables on the next pages we summarise the results, which are described in more detail below. **Please note that the numbers presented in this chapter are based on the search strategy described in Annex 3 (Data lock point was 31 December 2014).**

Table 7.1 Overview of approved advanced therapies in the four jurisdictions

	US	Canada	Japan	South Korea
Number of advanced therapies	5*	1	4	18
Other schemes	N/R	N/R	N/R	N/R
Features of the approval process	N/R	N/R	Fast Track (JACE), Orphan Designation (TEMCELL)	N/R
Therapeutic indication (ICD-10)				
1 Certain infectious and parasitic diseases	0	0	0	1
2 Neoplasms	2	0	0	3
6 Diseases of the nervous system	0	0	0	1
9 Diseases of the circulatory system	0	0	1	1
11 Diseases of the digestive system	1	0	0	1
12 Diseases of the skin & subcutaneous tissue	1	0	1	0
13 Diseases of the musculoskeletal system and connective tissue	1	0	1	2
19 Injury, poisoning and certain other consequences of external causes	0	1	1	9
Type of product used				
% Autologous/total	80,0%	0,0%	75,0%	88,9%
% Allogeneic/total	20,0%	100%	25,0%	11,1%
Status of approval				
Approval	5	0	3	18
Conditional approval	0	1	1	0
Medical device incorporated				
Yes	0	0	0	0
No	5	1	4	18
Reimbursement status				
Reimbursed	3	0	3	4
In process	2	0	1	0
Not reimbursed	0	1	0	9
Not reported/Not applicable	0	0	0	5
Size of developers				
Small	1	0	0	6
Medium	0	1	2	3
Big	4	0	2	6
Not reported/Not applicable	0	0	0	3
Type of developer				
Academia	0	0	0	0
Non-for-profit	0	0	0	0
Profit	5	1	4	18

* In October 2015, Imlygic (talimogene laherparepvec) was approved by FDA, resulting in a total of 6 advanced therapies that are approved in the US.

Table 7.2 Overview of ongoing research projects in the four jurisdictions

	US	Canada	Japan	South Korea
Number of ongoing research projects	132	39	131	43
Therapeutic indication (ICD-10)				
1 Certain infectious and parasitic diseases	4	0	0	1
2 Neoplasms	28	6	63	6
3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	7	1	1	1
4 Endocrine, nutritional and metabolic diseases	1	4	3	0
5 Mental and behavioural disorders	0	0	1	0
6 Diseases of the nervous system	10	1	0	6
7 Diseases of the eye and adnexa	5	2	5	2
8 Diseases of the ear and mastoid process	1	0	2	0
9 Diseases of the circulatory system	39	14	22	7
10 Diseases of the respiratory system	2	0	2	0
11 Diseases of the digestive system	3	0	6	6
12 Diseases of the skin and subcutaneous tissue	2	1	1	1
13 Diseases of the musculoskeletal system and connective tissue	16	0	11	8
14 Diseases of the genitourinary system	6	4	2	0
16 Certain conditions originating in de perinatal period	0	0	1	0
17 Congenital malformations, deformations and chromosomal abnormalities	1	2	7	0
18 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1	1	0	1
19 Injury, poisoning and certain other consequences of external causes	6	3	4	4
Type of product used				
% Autologous/total	43,2% (57)	53,8% (21)	46,6% (61)	48,8% (21)
% Allogeneic/total	21,2% (28)	23,1% (9)	8,4% (11)	37,2% (16)
% Not reported	4,5% (6)	2,6% (1)	26,0% (34)	2,3% (1)
% Not applicable	31,1% (41)	20,5% (8)	19,1% (25)	11,6% (5)
Tested in humans				
Yes	132	39	130	43
Not reported	0	0	1	0

	US	Canada	Japan	South Korea
Clinical phase				
Phase I	54	8	36	9
Phase I/II	38	13	65	14
Phase II	25	11	25	14
Phase II/III	2	1	2	1
Phase III	12	5	1	5
Not reported	1	1	2	0
% Early phase (phase I, I/II or II)	88,6% (117)	82,1% (32)	96,2% (126)	86,0% (37)
% Late phase (phase II/III or III)	10,6% (14)	15,4% (6)	2,3% (3)	14,0% (6)
Size of developers				
Small	7	2	0	3
Medium	19	12	13	4
Big	86	24	99	28
Not reported	20	1	19	8
Type of developers				
Academia	56	6	102	23
Non-for-profit	42	14	19	9
Profit	34	19	1	10
Not reported	0	0	9	1
% For profit	25,8% (34)	48,7% (19)	0,8% (1)	23,3% (10)
% Non-for-profit and academia	74,2% (98)	51,3% (20)	92,4% (121)	74,4% (32)
Involvement for profit organisations in late phase trials (phase II/III or III)	71,4% (10)	83,3% (5)	0,0% (0)	0,0% (0)
Year				
2008	15	1	16	3
2009	15	7	11	3
2010	16	3	13	5
2011	17	6	24	6
2012	23	7	18	9
2013	19	6	23	13
2014	27	9	26	4

7.2. United States

Ongoing research projects

In the US almost all ongoing clinical trials are registered at clinicaltrials.gov. Through desk research we identified 132 ongoing research projects on advanced therapies. Of these projects 39 are targeting diseases of the circulatory system, 28 neoplasms, 16 diseases of the musculoskeletal system and connective tissue and 10 diseases of the nervous system (the indication of the other ongoing research projects are listed in Annex 7). All the products have been tested in humans. From these projects 54 are in clinical phase I, 38 in phase I/II, 25 in phase II, 2 in phase II/III and 12 in phase III (1 developer did not report about the phase of the ongoing research project). 43,2% of the projects include an autologous product and 21,2% an allogeneic product (6 developers did not report about the type of cell/tissue product included). In 41 cases this product characteristic was not reported.

Most of the developers are academia (56), 42 of the companies are non-for-profit and 34 are for profit. 86 of the developers are labelled as big (>250 employees), 19 of the developers are labelled as medium (50-250 employees) and 7 of the involved developers are small companies (1-50 employees) (20 developers did not report about the size of their company). 71,4% (10) of the late phase (II/III or III) research projects are developed by for profit companies. Full information about the ongoing projects can be found in Annex 7.

Approved advanced therapies

In the US, the FDA approved several products as biologic drugs, of which six are cord blood products. These products do not meet the definition of advanced therapies as used in the report. In Table 7.3. we list the products that do meet the definition. Please note that Imlygic (oncolytic viral therapy) was approved (in October 2015) after we conducted the desk research and interviews for this study.

The full details of the 5 remaining products including brand name, developing company, availability, specific features about the approval process, the therapeutic indication that is being targeted, whether the product is autologous or allogeneic, whether or not a medical device is included and the reimbursement status of the product are shown in Annex 6. In this Annex we also give more information about the developing companies of the approved products, such as the size of the company, the type of organisation and the annual turnover.

Table 7.3 Approved advanced therapies in the US

Product	Company
Azficel-T	Fibrocell Technologies
Carticel	Genzyme Biosurgery
TheraCys	Sanofi Pasteur Limited
Gintuit	Organogenesis Incorporated
Provenge	Dendreon Corporation
Imlygic	Amgen

7.3. Canada

Ongoing research projects

Through desk research we identified 39 ongoing research projects on advanced therapies in Canada. Of these projects 14 are targeting diseases of the circulatory system, 6 neoplasms, 4 endocrine, nutritional and metabolic diseases and 4 diseases of the genitourinary system (the indications of the other ongoing research projects are listed in Annex 7). All the products have been tested in humans. From these projects 8 are in clinical phase I, 13 in phase I/II, 11 in phase II, 1 in phase II/III and 5 in phase III (1 developer did not report about the phase of the ongoing research project). 53,8% of the projects included an autologous product and 23,1% an allogeneic product (1 developer did not report about the type of cell/tissue product included). In 8 cases this product characteristic was not reported.

Most of the developers are for profit companies (19), 14 of the companies are non-for profit and 6 are academia. 24 of the developers are labelled as big (>250 employees), 12 of the developers are labelled as medium (50-250 employees) and only 2 of the involved developers are small companies (1-50 employees) (1 developer did not report about the size of their company). 83.3% (5) of the late phase research projects (phase II/III or III) are developed by for profit companies. Full information about the ongoing projects can be found in Annex 7.

Approved advanced therapies

In Canada one advanced therapy product is approved for commercialisation, this is Prochymal, developed by Osiris Therapeutics (Table 7.4). The full details of this product are provided in Annex 6.

Table 7.4 Approved advanced therapies in Canada

Product	Company
Prochymal	Osiris Therapeutics

7.4. Japan

Ongoing research projects

For Japan we identified 131 ongoing research projects, which target various diseases. However, 63 of the research projects are targeted at neoplasms, 22 at diseases of the circulatory system and 11 at diseases of the musculoskeletal system and connective tissue. 99,2% of the products have already been tested in humans (1 developer did not report about this subject). From these project 36 are in clinical phase I, 65 in phase I/II, 25 phase II, 2 in phase II/III and 1 in phase III (2 developers did not report about the clinical phase of the ongoing research project). 46,6% of the projects included an autologous product and 8,4% an allogeneic product. In 59 cases this product characteristic was not reported.

Most of the developers are academia (102), 19 of the companies are non-for-profit and 1 is for profit (9 companies did not report about this characteristic of the company). Based on the databases, the involvement of for profit companies is low, compared to the other three jurisdictions. This is due to the fact that the company responsible for the registration of a clinical trial is often a non-for-profit or academic organisation. However, in reality the product is developed through partnerships with for profit companies (see section 8.3.3).

99 of the developers are labelled as big (>250 employees), 13 of the developers are labelled as medium (50-250 employees) and none of the involved developers are small companies (1-50 employees) (19 developers did not report about the size of their company). None of the late phase research projects (phase II/III or III) are developed by for profit companies. Full information about the ongoing projects can be found in Annex 7.

Approved advanced therapies

Until 2015, there were 2 advanced therapy products approved in Japan: JACC and JACE developed by the company J-TEC. In September 2015 two new products were approved for commercialisation: TEMCELL and HeartSheet (Table 7.5). Full details of these products are provided in Annex 6.

Table 7.5 Approved advanced therapies in Japan

Product	Company
JACC	J-TEC
JACE	J-TEC
HeartSheet	Terumo Corporation
TEMCELL	JCR Pharma. Co.

7.5. South Korea

Ongoing research projects

Through desk research 43 ongoing research projects on advanced therapies were identified. In a recent presentation of the MFDS (2016), concerning regulatory activities in the field of advanced therapies in South Korea, a number of 200 clinical trials was mentioned. The difference in numbers may be explained by using a different data lock point (this report: 31 December 2014) and search strategy (databases/definitions used).

Of these 43 included ongoing research projects 8 are targeting diseases of the musculoskeletal system and connective tissue, 7 diseases of the circulatory system, 6 diseases of the nervous system and 6 diseases of the digestive system (the indication of the other ongoing research projects are listed in Annex 7). All of the products have been tested in humans. From these projects 9 are in clinical phase I, 14 in phase I/II, 14 phase II, 1 in phase II/III and 5 in phase III. 48,8% of the projects included an autologous product and 37,2% an allogeneic product (1 developers did not report about the type of cell/tissue product included). In 5 cases this product characteristic was not reported.

Most of the developers are academia (23), 10 of the companies are for profit and 9 are non-for-profit (1 company did not report about this characteristic of the company). 28 of the developers are labelled as big (>250 employees), 4 of the developers are labelled as medium (50-250 employees) and only 3 of the involved developers are small companies (1-50 employees) (8 developers did not report about the size of their company). None of the late phase research projects (phase II/III or III) are developed by for profit companies. Full information about the ongoing projects can be found in Annex 7.

Approved advanced therapies

In South Korea, there were 18 advanced therapies approved at the data lock point (see Table 7.6). Full details of these products are provided in Annex 6.

Table 7.6 Approved advanced therapies in South Korea

Product	Company
Cartistem	Medipost Co.
HeartiCellgram	FCB PharmiCell Co., Ltd.
Cupistem	Anterogen Co., Ltd.
LSK autograft	Chabio&tech
Neuronata-R	Corestem Inc.
Cureskin	S. Biomedics.
Queencell	Anterogen Co., Ltd.
Autostem	Chabio&tech
RMS Ossron	Sewon Cellontech Co., Ltd.
Hyalgraft-3D	Chabio&tech
NKM	NKBio
Immuncell-LC	Green Cross Cell
Adipocel	Anterogen
CreaVax-RCC	JW CreaGene
Keraheal	MCTT
Kaloderm	Tego Science
Holoderm	Tego Science
Chondron	Sewon Cellontech

8. Analysis of the economic aspects of the advanced therapies market

8.1. Introduction

In this Chapter, we provide an overview of the economic aspects of the advanced therapies market including:

- relevant IPR legislation (section 8.2);
- incentives to support developers of advanced therapies (section 8.3);
- the average approval procedure time and time to be reimbursed after approval of selected products per country (section 8.4); and
- a quick scan on pricing and reimbursement policies that exists in the jurisdictions under study (section 8.5).

8.2. Overview of relevant intellectual property rights legislation

For any patent, five elements must be addressed for patentability:

- Proper subject matter;
- Novelty: A claimed invention is not patentable if the invention was already described in a printed publication, is publicly used or available in a different way to the public before the effective filing date of the claimed invention;
- Non-obviousness (US, inventive in Europe): A claimed invention is not patentable if the differences between the claimed invention and earlier inventions are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention (to a person having ordinary 'skill of art to which the invention pertains');
- Utility (US; industrial applicable in Europe);
- Proper disclosure: A disclosure which has been made 1 year before the effective filing date of a claimed invention shall not be 'prior art' (patentable) to the claimed invention under certain circumstances. The same applies for disclosures appearing in applications and patents. A proper disclosure depends on several factors.[1]

The patent must be provided with a specification (written description) which enables the invention to be made and used. A patent is usually granted for 20 years.

Below, we provide an overview of relevant IPR legislation as well as any landmark case law that may exist per country. The following aspects are addressed: 1) whether substantially manipulated cells are patentable and 2) whether there are instruments in place other than patents to protect the investments of developers of advanced therapies. The overviews have been verified by relevant stakeholders, including representatives of patent offices and researchers in the relevant fields.

8.2.1. United States

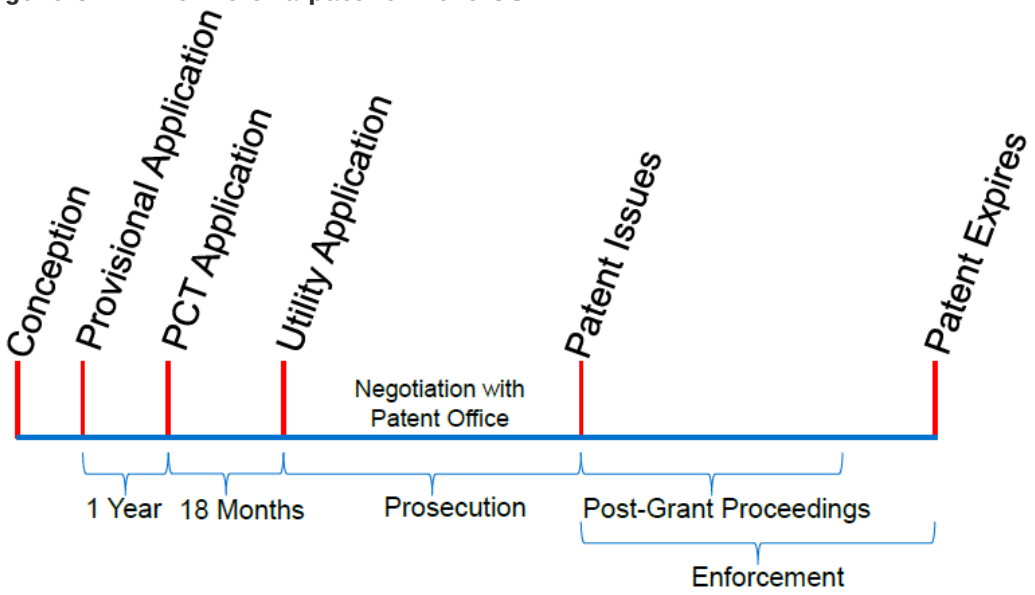
In the US, the responsible body for granting patents for the protections of inventions and to register trademarks is the United States Patent and Trademark Office (USPTO).

The US patent law specifies the 'subject matter' for which a patent may be obtained and the specific conditions for patentability. US patent law appears to be in a state of

change and particularly in the area of biotechnology there is uncertainty whether an invention is patentable or not.

Patents in the US have a certain term, which is displayed in the timeline below. Patents filed before June 8, 1995 have 17 years of patent protection. Patents, which are filed after June 8, 1995, have 20 years of patent protection.[2] Regenerative medicinal products are provided with a maximum patent term of 25 years (i.e., exception in US patent law).[3]

Figure 8.1 Timeline of a patent in the US[4]



Patent protection for human genes is also applicable to advanced therapies. The US Supreme Court has 'removed' three decades of patent protection for human genes to accelerate discoveries. However, the protection was mainly focused on genetic testing (tests for breast cancer and ovarian cancer) and not targeting gene therapy.[5]

Intellectual property rights are difficult to apply to the field of stem cells (research) because of the associated complex cellular differentiation.[6] In addition, stem cells have their origins in specific human donors. This is the most important difference for patenting of synthetic innovations.

Landmark case laws also exist regarding advanced therapies in the US. These include "Supreme Court Decision in Association for Molecular Pathology v. Myriad Genetics, Inc." and "2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting of Involving Laws of Nature/Nature Principles, Natural Phenomena, and/or natural Products". Under the latter landmark case law, a specific guidance was used for 'all claims (i.e. machine, composition, manufacture and process claims) reciting or involving laws of nature/natural principles, natural phenomena, and/or natural products'. There are a number of bills, which are still pending (See Annex 10).

Are substantially manipulated cells patentable?

Within the US, the patent landscape for stem cell research differs between individual states.

In 1987, the USPTO stated that they 'officially consider non-naturally non-human multicellular living organisms, including living animals, to be patentable'.[6] From this moment onwards, any biological interventions that required human interventions were patent eligible. A more recent patent reform (regarding Section 33 of the American Invents Act) made claims directed to or encompassing a human organism not patent-eligible. On 16 September 2011, the statutory exclusion was enacted and applies to any application for a patent that is pending on, or filed after 16 September 2011.[7] This Act does not change existing law; it codifies existing policy of the USPTO.

According to the USPTO, it is possible that a substantially manipulated cell is patentable if the cell is novel, non-obvious and has utility (elements for patentability). The patent application also needs to meet the other patent requirements for patentability, such as proper disclosure.[1*,8]

Because of the use of stem cells in the field of regenerative medicine, the USPTO has recognized inventions with stem cells as patent eligible. The patent eligibility mainly depends on the extent of human manipulation of the stem cells and how this can be translated into a meaningful claim for a patent.[7] If the cells are not manipulated in a significant way, they might be seen by the court as a 'product of nature' and therefore not patent eligible. This means that the way in which cells are manipulated and changed from their natural state is important for the patent eligibility.

Induced pluripotent stem cells (iPS) are cells which have the ability to differentiate into any cell and are a valuable alternative for human embryonic stem cells (iPS were announced in November 2007).[9] iPS are patent eligible in the US under specific conditions. iPS methods are patent eligible if these claim steps of isolating and reprogramming patient's somatic cells into a pluripotent state (iPS). In addition to this, the iPS have to be differentiated in reprogrammed cloned somatic cells, tissues or organs and should be used in personal medical treatment.[7] In conclusion, substantially manipulated cells are patentable in the US as long as a claim is not encompassing a human being.

Are there instruments other than patents to protect the investments of developers of advanced therapies?

There are several instruments available to protect the investments of developers of advanced therapies in the US. One of them is trade secret protection. Trade secret protection is an alternative to a patent and provides a supplementary right to IPR legislation because it can be used to protect information among the research, development and testing stage of the product.[10]

In addition, if the advanced therapy is a biologic subject matter to the approval of the FDA, exclusive marketing rights might protect the investment. Different types of exclusivity exist and the exclusivity may ran concurrently with a patent or not.[2,11] For example, a New Chemical Entity (drug) (NCE) receives data exclusivity for 5 years. During this period FDA will not review any 'abbreviated NDAs or 505(b)(2) applications for a drug containing the same active moiety' (although there is possibility to submit an application after 4 years if the ANDA contains a 'certification of patent invalidity or noninfringement'). An approved orphan drug receives market exclusivity for 7 years. During this period the FDA will not approve 'any other application for the same drug for the same orphan disease or condition'. Biological products (e.g. stem cells) receive data exclusivity for 12 years.[2*] During this period, starting from the date on which the reference product was approved, the FDA will not approve an application for a

[1*] Information provided through e-mail (FDA).
[2*] Interview with an expert in the field of intellectual property (US).

biosimilar or interchangeable product. Also, an application may not be submitted to FDA for review until 4 years after the date on which the reference product was approved.[12]

The Patient Protection and Affordable Care Act of 2010 amended the Public Health Service Act to provide a more simplified procedure for biological products that are biosimilar to FDA licensed products. Some products are provided with 12 years of data protection during which a biosimilar product cannot rely upon the safety and efficacy data of the original product for FDA approval.[3]*

8.2.2. Canada

In Canada the responsible body for granting patents and processing intellectual property is the Canadian Intellectual Property Office (CIPO). It is comparable with the USPTO in the US. Both bodies maintain a comparable patent law. The biggest difference regarding patentability of biotechnology products between the US and Canada is that stem cells have been patentable in the US until 2007,[9] but have never been patentable in Canada.

Are substantially manipulated cells patentable?

Not all substantially manipulated cells are patentable. Whether substantially manipulated cells are patentable depends on the origin and the features of the substantially manipulated cell(s). In Canada, a somatic cell taken from an organism that is cultured outside the body (e.g. tissue engineering), is patentable. The CIPO makes a difference between unicellular (lower life form) and multicellular (higher life form).[13] Human embryonic stem (hES) cells are not (and have never been) patentable in Canada because these cells might develop into a higher life form (same for fertilized eggs and totipotent (differentiating) stem cells).[14] Induced pluripotent cells (iPS) differ from hES cells in a way that iPS cells are deployed from somatic cells.[15] The iPS cells are reprogrammed to an embryonic state.[16] Pluripotent and multipotent induced stem cells, which do not have the ability to develop into a higher life form are patentable in Canada.[17] Groups of cells, which are also patentable are e.g. sperm cells, (transducing) vectors, ova cells and retinal cells (derived cells).

Are there instruments other than patents to protect the investments of developers of advanced therapies?

When an advanced therapy product enters the market, there is often 4 or 5 years left of the patent protection period.[4]* There are two main instruments in Canada to protect the investments of developers, including those of advanced therapies. The first is trade secret protection, which is already elaborated in the US section. A second instrument to protect investments of developers is data protection. Data protection provides an eight year-term of protection to innovative drugs in a way that it prevents other companies from using the data of developers. Companies introducing a new product/drug containing a new medical ingredient, which is not earlier approved by Health Canada and is not a variation of earlier approved products, are entitled to this 8-year period of exclusivity.[18] During this period, a manufacturer may not file a drug submission or referencing a new drug within 6 years after authorisation of the innovator drug.[19]

A Notice of Compliance (NOC) is a notification, indicating that a manufacturer has complied with the sections C.08.002 or C.08.003 and C.08.005.01 of the Food and Drug Regulations (see section 4.3.1.).[19] Under section C.08.004.1 of the Food and Drug Regulations, a manufacturer who seeks a NOC based on a direct or indirect

[3]* Interview with a representative of the patent office (US).
[4]* Interview with an expert in the field of intellectual property (Canada).

comparison with the innovative product is not allowed to file a submission before the end of a period of six years after the day on which the first NOC for the innovative new product was administered. In addition to this, the NOC cannot be issued before the end of the period of 8 years after the first NOC was issued to the innovator.[18]

Submission to the patent list in Canada is not obligatory. Even if a drug or product has received marketing authorisation in Canada, a patent may not be listed on the Patent Register for that drug or product.[19] An example is Prochymal.

8.2.3. Japan

In Japan the responsible body for administering the industrial property right system is the Japan Patent Office (JPO). This system has become increasingly important to promote the progress of the overall industrial progress (i.e. biotechnology) in Japan.

According to the Japanese Patent Act, an 'invention' is "the highly advanced creation of technical ideas utilizing the laws of nature". If the invention is not covering this definition, it is not patentable. This invention needs to be "highly advanced" to differentiate it from a device.

Are substantially manipulated cells patentable?

Discoveries of natural things or natural phenomena, for which an inventor 'does not create any technical idea with intention' are not considered an invention. Article 29(1) of the Patent Act states, however, that 'if things in nature such as chemical substances or microorganisms have been isolated artificially from their surroundings, those are creations and considered as an invention' and are therefore patentable. In Japan it is only possible to receive a patent when a product is material based only (i.e. not for a method).

Patent article 32 defines unpatentable inventions. Examples of such inventions include 'human themselves produced through genetic manipulation'.[20]

According to the 'Examination Handbook for Patent and Utility Model in Japan', biological inventions are 'inventions relating to matters consisting of or comprising biological material, or processes of producing, treating or using the biological material'.[21] Biological materials include: nucleic acids, polypeptides, microorganisms (stem cells, dedifferentiated cells and differentiated cells) and animals and plants. Regarding to substantially manipulated cells, the following needs to be described to show that a cell, such as an iPS cell, can be produced in an invention relating to the differentiated cell:

- The factor contributing to dedifferentiation of the differentiated cell (reprogramming factor);
- A species of cell in which the reprogramming factor is introduced;
- A process of introducing the reprogramming factor;
- A condition of culturing the cell in which the reprogramming factor is introduced;
- A process of selecting the dedifferentiated cell;
- Means for identifying the dedifferentiated cell.[21]

If a stem cell itself has novelty or a process of inducing differentiation has novelty, and it cannot be distinguished from the publicly known differentiated cells as a product, an invention of the obtained cell does not have novelty. In 2009, the Japanese government and the JPO prepared an examination guideline regarding iPS. In addition, the Japanese government described the protection of human stem cells by

intellectual property law in the same year.[22] Japan was the first country in the world to grant a patent in iPS (27th November, 2008).[23]

Chapter 3 of the 'Examination Handbook for Patent and Utility Model in Japan' describes the patent applications relating to medical inventions. A medical invention is described as an 'invention of a product which provide a new medicinal use, based on the discovery of an unknown attribute of the material' (component used as an active ingredient, including a compound, a cell or a tissue). Because a medical invention is 'an invention of a product' and therefore not included in 'methods of surgery, therapy or diagnosis of humans', it is identified as an 'industrially applicable invention' and patentable.[24] This also applies to the following types of methods:

- Methods for manufacturing a medicinal product by utilizing raw material collected from the human body. Examples include blood preparation, vaccine genetically modified preparation and cell medicine;
- Methods for manufacturing a medical material by utilizing raw material, which is collected from a human body. Examples are artificial bone or cultured skin sheets;
- Methods of manufacturing an intermediate product for a medicinal product or a medical material by utilizing raw material, which is collected from a human body. Examples are methods for differentiation and introduction of cells, methods for separation and purification of cells;
- Methods for analysing a medicinal product or a medicinal material, or intermediate product of this, which is manufactured by utilizing raw material, and which is collected from a human body.[25]

On February 24, 2014 the Japanese government announced that, patent extension of regenerative medicine products in Japan can be granted for up to 5 years, which is common for medical devices and pharmaceuticals. This patent extension is primarily instigated to allow companies to collect safety data and is therefore subject to conditional and time-limited approval.[26]

Are there instruments other than patents to protect the investments of developers of advanced therapies?

The number of domestic patents is rising and the Japanese inventions in regenerative medicine cover 63.2% of all patents for therapeutics between 2002 and 2006. This percentage (for Japanese inventions) was much lower in the US and Canada.[27]

As in the US and Canada, trade secret protection exists in Japan via the 'Unfair Competition Prevention Act'. In Japan a trade secret is defined as 'any production method, sales system or other useful or technical or operational information related to business activity that is not known to the public and that has been kept in confidence'.[28] Inventions that can be easily copied, or methods or processes that are too difficult to patent, are better kept as trade secrets. Keeping these as trade secrets might be better than being disclosed to the public as required under a patent registration.[29]

In Japan a period of data exclusivity for new medicines exists in which no marketing application for generics can be issued. The re-examination term for a new active ingredient is 8 years plus the period of a generic drug application and its approval. For orphan (or paediatric drugs) a period of 10 years applies plus the period between generic approval and its price listing.[30]

8.2.4. South Korea

In South Korea the responsible body for processing IPR and granting patents is the Korea Intellectual Property Office (KIPO).[31] The patents can be found via the Korea Intellectual Property Rights Information Service (KIPRIS). The Patent Act in South Korea is instigated in South Korea to encourage, protect, and utilize inventions and thereby promoting the development of technology, and to contribute to the development of industry.[32]

Are substantially manipulated cells patentable?

The South Korean Patent Act covers the legislation regarding patentability and patents in South Korea. There are no specific articles regarding the patentability of substantially manipulated cells. The following articles can be applicable to the patentability of substantially manipulated cells:

- Article 29 Requirements for Patents Registration;
- Article 30 Inventions not Deemed to be Publicly Known;
- Article 32 Unpatentable inventions.[33]

Inventions are novel if they fulfil the following requirements. The invention may be patentable unless the invention is publicly known in the Republic of Korea or in a foreign country prior to the filing of the patent. In addition, patents described in a publication distributed in the Republic of Korea or in a foreign country prior to the filing of the patent is also not patentable according to the Patent Act.[34] A patent shall also not be granted if an invention could easily be made by a person having ordinary 'skill in the art to which the invention pertains'.[35] When an invention is identical to an invention or device described in 'specifications or drawings initially attached to another patent application', a patent will not be granted.[36] Patentable inventions need to to be filed within 12 months from the moment when the invention is first known to the public. In this case, the invention will be treated as 'new' even though it was already disclosed to the public.

Inventions are unpatentable in South Korea when these inventions (in the field of genetic engineering) 'are feared to have risks to contravene public order or morality or to injure public health'.[37]

In South Korea, the use of stem-cell derivatives and iPS cells is increasing. The KIPO applies the same statutory patentability requirements to stem-cell related inventions as to other types of patents.[38]

Although there is no specific IPR legislation on the patentability of substantially manipulated cells, multiple patents have been granted for substantially manipulated cells. Below we provide some examples of such patents (Table 8.1):[38]

Table 8.1 Patent numbers

Patent No.	Description of patent
Patent No. 100494265	Composition for treatment of articular cartilage damage.
Patent No. 101114800	Composition comprising mesenchymal stem cells or culture solution of mesenchymal stem cells for the prevention or treatment of neural diseases.
Patent No. 101135636	Method for producing mesenchymal stem cells from human pluripotent stem cells and mesenchymal stem cells produced by thereof.
Patent No. 100985832	Method for culturing human embryonic stem cells.
Patent No. 1066773	Method for isolation of inner cell mass and method of preparation of embryonic stem cell lines using inner cell mass isolated by the same.

Are there instruments other than patents to protect the investments of developers of advanced therapies?

In South Korea IPR legislation can help to incentivise investment in R&D. Between 2005 and 2011 the South Korean patent office granted 37 stem cell cosmetic patents.[39] IPR might also help to build scientific capacity.

In addition to patents (IPR legislation), trade secret protection exists to protect the investments of developers in South Korea. In South Korea, trade secret is defined by the Unfair Competition and Trade Secret Protection Act (UCPA) as 'information of a technical or managerial nature that can be used in business activities'. In addition, a trade secret is generally unknown to the public, it possesses independent economic value and is kept secret (by the owner).[40] Due to the perceived lack of protection of national core technologies (because the UCPA only protects trade secrets of private companies) the Industrial Technology Act was enacted (applies to acts committed on or after April 28, 2007).[40] The aim is to increase the protection of domestic industrial technology and to prevent certain 'key technologies' from going outside Korea. National security and technological development were promoted in this way.[41]

According to Korean Patent Law, data exclusivity of six years is provided to new drugs and four years to drugs which are identical to already licensed drugs. Under the South Korea-US Free Trade Agreement five or three years of data exclusivity is granted for information regarding safety and efficacy submitted in support of the marketing approval of medicines. Five years of data exclusivity applies to 'all safety and efficacy information submitted in the process of marketing approval if the origination of this information involves a considerable effort'. Three years of data exclusivity applies to 'all new clinical information that is submitted in the process of obtaining marketing approval for a product containing a chemical entity'.[30]

8.3. Incentives to support developers of advanced therapies

There are several hurdles mentioned with regard to the marketing authorisation and reimbursement of advanced therapies. These include:

- Challenges with regard to developing autologous products, such as complying with Good Manufacturing Practice (GMP) protocols as many developers of advanced therapies are small (often universities or small start-ups) with limited resources;[42]
- The regulatory requirement to establish and maintain product comparability when changes are made to the manufacturing process or the use of advanced therapies is

scaled to multiple sites. For example, due to variability of the starting material (derived from donors) it may be difficult to establish comparability;[42,43]

- Advanced therapies are often developed for niche indications and the number of patients available for studies can be small and insufficient to power a superiority trial;
- Advanced therapies can be combinations of devices, procedures and therapies; this makes the assessment of benefit/risk complex.[44]

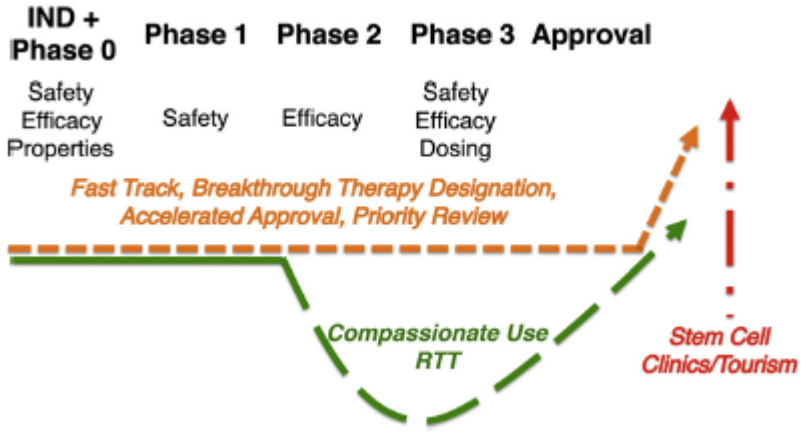
In addition to IPR legislation (see section 8.2), several other incentives exist in the selected jurisdictions to support developers of advanced therapies. These are described in more detail below.

8.3.1. United States

There are several federal agencies that fund(ed) regenerative medicine research. The largest funding agency is National Institute of Health (NIH) (US$2.54 billion from 2012-2014; i.e. 2,24 billion euro). The Department of Defence (DOD) is the second largest funder of regenerative medicine research and active in multiple regenerative medicine projects followed by the Department of Veteran Affairs (VA).[45]

In addition to federal funding, there are multiple regulatory pathways to accelerate the review of advanced therapies to decrease the time to marketing authorisation for manufacturers. These expedited programmes might be used as potential ways for a faster availability of advanced therapies.[46] The mechanisms include 'Fast Track', 'Break Through Therapy Designation', 'Accelerated Approval' and 'Priority Review'.[47] These mechanisms were primarily applied to chemical based drugs but are also applicable for accelerating the clinical trial process of advanced therapies (see section 3.3.2). In addition to the use of the four expedited programmes, expanded access is discussed as a way to accelerate the clinical trial process of advanced therapies (see section 3.6).[46] Figure 8.2 displays the use of accelerating mechanisms by the FDA for drugs and advanced therapies.

Figure 8.2 Accelerating mechanisms FDA. Source:[46]



Orphan Drug Act (ODA)

To provide financial incentives to developers of orphan drugs, a special Act was initiated.[48] The associated benefits under the Orphan Drug Act for rare disease therapies include: annual grant funding and tax credits (to defray the cost of qualified clinical research and testing), assistance in clinical research study designs, seven years of market exclusivity after approval of the orphan drug, and a waiver of the

Prescription Drug User Fee Act (PDUFA) filing fees, this fee was more than US$1.3 million (1.1 million euro) per application (2015). All these benefits should encourage companies to invest in the development of drugs for rare disease indications with high-unmet need.[49]

The Rare Paediatric Disease Priority Review Voucher (RP-PRV) programme

In 2012 the FDA developed a programme to support the development of drugs for rare paediatric diseases (diseases of which half or more occur in patients below the age of 19): the Rare Paediatric Disease Priority Review Voucher (RP-PRV) programme, section 529 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act).[50] The programme became active in 2014-2015 and includes that when a company is granted regulatory approval for a drug aimed at a paediatric rare disease it receives a RP-PRV. The voucher provides the holder two options: (1) to expedite the review of any future product (orphan drug or high volume market drug) from their own pipeline, or (2) sell the voucher to any other company, which can use it to expedite any product from their pipeline. Selling the voucher generates a huge cash income, which then can be used to develop a new product.

Using the voucher to expedite the FDA review of any New Drug Application (NDA) or Biologics License Application (BLA) will shorten the review time: instead of 18 months (average) the review will take place within six months. This can help a company to achieve first-to-market status, which generates many pricing and market-share advantages. Until now, six RP-PRVs have been awarded, from which three have been sold for US$67.5 million (59.4 million euro), US$250 million (220 million euro), and US$350 million (308.5 million euro).[51]

One remark: the programme is operating on a trial basis; once three RP-PRVs were awarded the Government Accountability Office (GAO) has one year to evaluate the program's efficacy and impact on the development of new drugs for rare paediatric diseases. After the evaluation (2016), the Congress can make the programme permanent.[49]

Networking and research programmes

There are also initiatives in place to accelerate clinical research. The American Medical Association established the Scientific Excellence through Exploration and Development (SEED) grant programme to encourage researchers in the field. One important result of the SEED programme is the possibility to apply for external funding (one of the biggest hurdles for manufacturers).[52] In 2006 the California Institute for Regenerative Medicine (CIRM) used the SEED programme for funding of their research because federal funding of human embryonic stem cell research was restricted.[53] This indicates that the SEED programme is important for the funding of research in the area of advanced therapies.

Recently, CIRM introduced a new way of funding research. This programme offers a financial incentive to researchers to advance their projects from basic or discovery level into the translational phase. The purpose of this programme is to create a pipeline of the most promising stem cell research that can move forward to a clinical trial.[54]

Furthermore, the Office of Cellular, Tissue and Gene therapies (OCTGT) has developed a website/programme for the developers of advanced therapies (OCTGT Lean). This webpage provides information on how to develop safe cellular and gene products of good quality.[55]

In addition, the Centre for Biologics Evaluation and Research (CBER) of the FDA provides regulatory oversight of clinical studies, proactive scientific and regulatory advice to medical researchers and manufacturers in the area of novel product development.[56]

8.3.2. Canada

To encourage the development of medicinal products for rare diseases, an orphan drug framework is currently being established in Canada.[57]

Other incentives to support developers of advanced therapies in Canada primarily exist of funding initiatives, research programmes and networking.[58]

Networking and research programmes

The Centre for Commercialization of Regenerative Medicine (CCRM) provides support for the clinical development of regenerative medicine. This organisation is supported by the Centres of Excellence for Commercialization and Research (CECR) programme, which is a federal programme.[58] The programme, created in 2007, provides funding opportunities to developers in order to bring innovations earlier to the market. This programme does not only focus on advanced therapies but also on the development of other research areas. Costs, which are generally not covered by other federal research funding programmes, are covered by the CECR programme. By including companies, academic institutions, non-for-profit organisations and other organisations in the programme a network for innovation is created. Via this network, external (foreign) investors are attracted as funding source to support developers of advanced therapies as well as other new technologies. The programme invests US$30 million (26.4 million euro) per year in Canadian innovation.[59] One network focussing on the development of advanced therapies with stem cell research is the Stem Cell Network (SCN). This network is funded by the Networks of Centres of Excellence (NCoE) from 2001 to 2016. The NCoE has brought together researchers, bioengineers and other professionals to move stem cell research in Canada forward.[58] The SCN has supported research and training of more than 1,800 highly qualified personnel. Currently twelve SCN-funded projects have entered the clinical trial phase.[60]

Another network stimulating stem cell research is the Canadian Stem Cell Foundation, which is an independent, non-for-profit charitable organisation. The foundation creates partnerships between scientists, business and community leaders and the public to accelerate the process of turning stem cell research into clinical applications and therapies.[58,61]

The MaRS Excellence in Clinical Innovation Technology Evaluation (EXCITE) programme is part of the MaRS Health portfolio. The purpose of this programme is to connect health technology innovators with experienced, award-winning researchers to obtain the evidence and data needed to show the value of the new product. Moreover, it is meant to start discussions between developers and relevant health system stakeholders to determine what information is needed to get the product successfully adopted. The EXCITE programme results in robust evidence, the so-called EXCITE core evidentiary bundle, which can be used for assessments and reviews by Health Canada early in the product lifecycle when re-development is still an option. They can also be used for reimbursement reviews (see section 8.5.2).[5*,62]

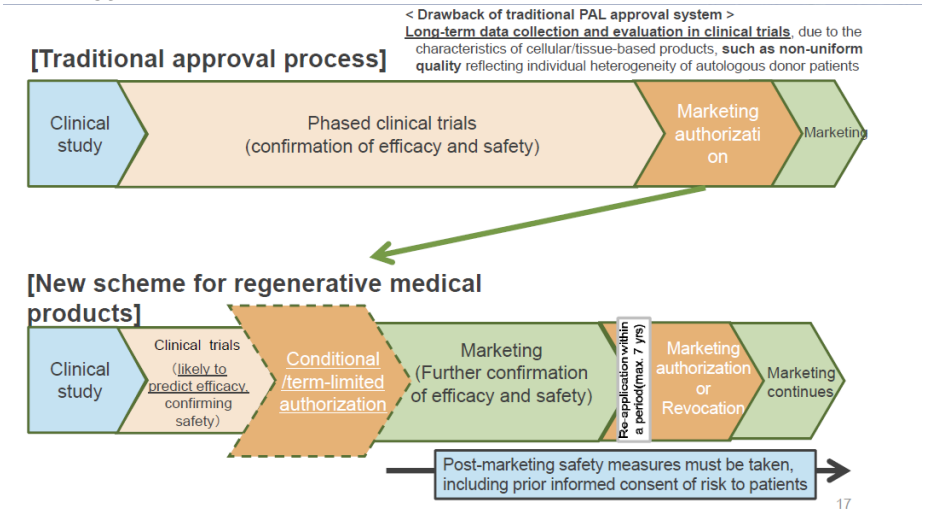
[5*] Interview with representative of body responsible for reimbursement/pricing of medicines (Canada).

8.3.3. Japan

In Japan conditional approval is available for *regenerative medicine products* (see section 5.3.1).[63] It is comparable to the expedited programmes in the US. As in the US, the focus is on shortening the current approval time - see section 8.4.

The procedure of the system for regenerative medicine under the PMD Act is shown in Figure 8.3.

Figure 8.3 Scheme of expedited approval system for regenerative medicine under the PMD Act[64]



The new marketing authorisation procedure for regenerative medicine enables developers to use surrogate endpoints, or an effect on a clinical endpoint other than survival or irreversible morbidity,[64] and a heterogeneous patient population in one study group to demonstrate probable efficacy (see section 5.3.1). After conditional approval is obtained, sponsors are required to perform large post-marketing clinical studies to confirm safety and efficacy, and other post-marketing safety measures.

The advantage of this system is that marketing authorisation allows a product to be available and reimbursable while gaining additional safety and efficacy data for the final approval. Within seven years after conditional approval, the developers have to resubmit the application for a full market authorisation with proofing safety and effectiveness. A concern regarding this regulation is that once a product is reimbursed during the conditional approval it might be difficult to reverse this if full marketing authorisation is not granted.[58]

Regulatory pathway for orphan products

Regenerative medicine products can also qualify for the regulatory pathway that applies to orphan products, when the regenerative medicine product is used to treat rare diseases. A regenerative medicine product is designated as orphan product when: (1) the prevalence of the disease covered by the product is less than 50.000 patients in Japan and (2) the product will be extremely beneficial from a medical standpoint when approved (PMD Act Article 77-2 and MHLW Ministerial Ordinance for the Enforcement of the PMD Act Article 251).[65] The advantage is that products with an orphan drug designation can be reviewed with priority (PMD Act Article 23-27(7)) (see section 5.3.2). Drug approval reviews generally occur in the order that applications are received. Orphan drugs get priority review after an evaluation of the seriousness of the targeted disease and the clinical usefulness of the product (Article 14-(7) of the Pharmaceutical Affairs Law).[66]

Moreover, sponsors can benefit from financial aid and tax relief on research expenses, guidance and advice and extension of the re-examination period from the conventional six years to a maximum of 10 years for drugs and from four years to maximum eight years for medical devices.[67]

Tax incentives exist for Japanese entities that are exclusively engaged in R&D activities; it permits a qualifying entity to subtract 20% of its income, which is attributable to the approved business activities for the first five years of receiving the research centre designation.[68] The Japanese tax exemption programme is also attributable to pharmaceutical products, including regenerative medicines.[6]*

Networking and research programmes

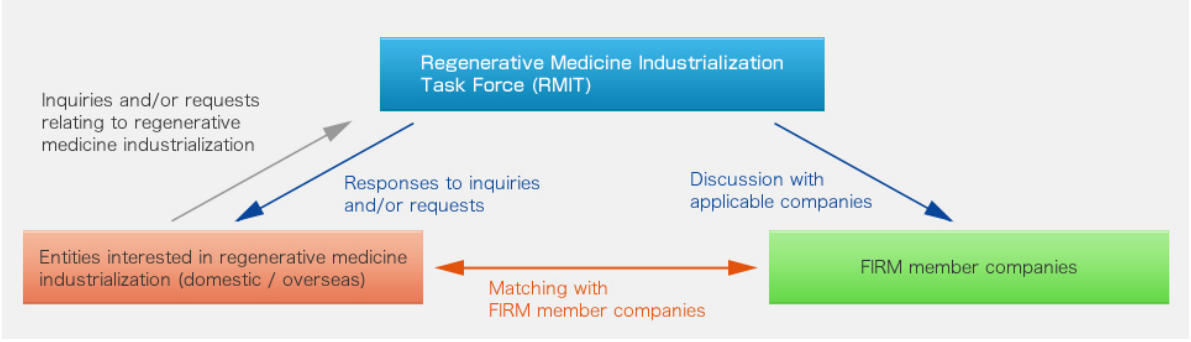
The Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST) aims to advance leading-edge research and development, which will strengthen Japan's international competitiveness while contributing to society and people's welfare through the application of its results.[69] The fund (100 billion Japanese Yen; 781 million euro) is managed and operated by the Japanese Society for the Promotion of Science (JSPS). One of the subsidised projects is the iPS Cell Project for Regenerative Medicine, carried out by the Kyoto University (5 billion Japanese Yen;39 million euro).[69]

The Regenerative Medicine Industrialization Task Force (RMIT) has been established in April 2015 under the Forum for Innovative Regenerative Medicine (FIRM). FIRM is an industry association, created to ensure safe access to the benefits of research into regenerative medicine. Over 170 companies are currently affiliated with FIRM. FIRM seeks to pave the way for breakthroughs in regenerative medicine. It tries to be the connector between the industry, governments and universities and engages with the media for the purpose of building consensus on the commercialisation process and the application of new regenerative medicine techniques.[70,71]

Several FIRM members worked together to establish an industrialisation support team. The ultimate goal of the support team is to serve patients in need of break-through therapies by accelerating application of the technologies.[72]

The relation between RMIT, FIRM and other entities, with related activities is shown in Figure 8.4.

Figure 8.4 Relation between RMIT, FIRM and other entities[70]



The Japanese government enacted two different Acts on May 2014 to promote medical research and development for i.e. regenerative medicine. These acts are the Act on the Incorporated Administrative Agency for Medical Research and Development and the Act to Promote Healthcare and Medical Strategy. Under this last Act the Agency for

[6]* Interview with a developer (Japan).

Medical Research and Development (AMED) was established in April 2015 as the new National Research and Development Agency. The AMED aims to incorporate all the work currently operated by the Ministry of Education, Culture, Sports, Science and Technology (MEXT); MHLW, and the Ministry of Economy, Trade and Industry (METI), either or not through organisations including Japan Science and Technology Agency (JST), National Institute of Biomedical Innovation (NIBIO), and New Energy and Industrial Technology Development (NEDO).[65]

The AMED promotes R&D in the field of medicine, from basic research to clinical trials, including regenerative medicine. It ensures establishing, maintaining and providing funding for integrated R&D through to practical application. AMED gives support in a variety of ways: initiatives for the prevention of research misconduct in order to ensure proper research, support for research institutes working to secure intellectual property, support for corporate alliances targeting practical application, and support for international joint research.[73]

8.3.4. South Korea

In Korea two alternative regulatory pathways for cell therapy products and gene therapy products exists: the orphan drug designation pathway and the conditional approval scheme for oncology treatment (see section 6.3.2).

Orphan drug designation

The orphan drug designation is regulated under the *Regulation on Designation of Orphan Drugs.* Conditionally approval is available for those products that target a disease or condition, which is life threatening. Conditional approval includes confirmatory post-marketing studies to demonstrate safety and efficacy, and implementation of a Risk management Plan (RMP). The completion of the application process for orphan drugs takes around 6 to 9 months. Orphan drugs are granted for exclusive marketing rights for 6 years, which is meant to encourage the research and development of orphan drugs.[74] Moreover, applications for orphan drugs may receive a 50% price reduction from the normal drug application fee.[75]

Safety testing

Another incentive is related to safety testing of cell therapies. The re-examination and the re-evaluation system to monitor the safety of medicinal products is different for cell therapies. After marketing authorisation the developer needs to submit a re-examination plan to the MFDS to identify potential adverse events. For this purpose, new medicinal products need to investigate 3000 cases within 6 years, cell therapies need to investigate 600 patients in 6 years.[76]

Networking and research programmes

Six different ministries of South Korea invest in research into stem cells and regenerative medicine. Especially the Ministry of Health and Welfare is expanding their support for clinical research on stem cells. In 2012 the Ministry of Health and Welfare gave a funding boost of 33 billion won (25 million euro), the total investment of the six ministries in the same year was 100 billion won (83 million euro). The investment is meant to link basic research to intermediate or clinical studies, after which the developers seek to commercialise the research at an early stage.

The research funding is specifically targeted to two areas: (1) rare or incurable diseases, as the incentive for the private sector is relatively low to invest in these diseases, and (2) common chronic conditions, to promote the South Korean companies to capture a bigger part at the global market.[77]

The Korea National Institute of Health (KNIH) is a research institute from the Korean government, which consists of 4 centres and 21 divisions with the focus on biomedical research. The KNIH aims to support stem cell and regenerative medicine research by establishing a national infrastructure. In 2013 the KNIH had a stem cell budget of 5 million US$ (4.4 million euro), the Ministry of Health and Welfare added another 42 million US$ (27 million euro) to this budget.[78]

The National Centre for Stem Cell and Regenerative Medicine (NCSR) is part of the KNIH, which aims to support and facilitate creative regenerative medicine research by establishing global standards, high-quality stem cell resources and information.[79]

8.4. Time to approval and reimbursement

In the previous sections we discussed the relevant IPR legislation and the incentives to support the developers of advanced therapies in the four jurisdictions. In this section we provide an overview of the time to approval and reimbursement of advanced therapies, and in particular for selected products per country. The information is collected through desk research and through interviews with relevant stakeholders.

The period from research and development (R&D) to a reimbursed advanced therapy is in general up to 20 years.[42] The outcomes of clinical research are the main input for the decisions about approval and commercialisation.[80] However, in some cases, the clinical trials are still ongoing when an advanced therapy is approved (conditional approval).

The processes are different in all four jurisdictions, but the main phases are the same. The first phase is the R&D phase, consisting of product development and basic non-clinical and clinical research. In this phase the developer could submit a patent application for the advanced therapy. The second phase is the granting of the marketing authorisation. The third phase concerns (pricing and) reimbursement.

Figure 8.5 Process towards reimbursement

Note: throughout this section the term “time to approval” measures the time that elapses from the time when clinical trials start until a marketing authorisation is granted. Basic research and preclinical studies are not accounted for. The term “time to reimbursement” reflects the time from the marketing authorsisation until the advanced therapy is reimbursed.

8.4.1. United States

Time to approval

The time from development to approval of advanced therapies is typically long compared to other medicinal products.

In this section, we describe the time to approval and reimbursement for Provenge in more detail as this is one of the selected products for this study. On December 22, 1996 Provenge was submitted to the IND and as the BLA on August 21, 2006 after

completing clinical trials. On April 29, 2010, the company (Dendreon) received full marketing authorisation resulting in a total time to approval of 14 years for Provenge in the US.[81] Table 8.2 provides a more detailed overview regarding the time to approval for Provenge while Annex 6, Table A6.2 provides information on all approved products in the US.

Time to reimbursement

In the US, currently 6 products are authorised for commercialisation. Of the 5 products included in the study, 3 products are reimbursed (Theracys, Gintuit and Provenge). Two products (Azficel and Carticel) have a reimbursement status which is unknown. The US system leaves the decision for reimbursement to the different health plans (see section 8.5).

With regard to the Provenge, we found the following. On July 1, 2011, the Centre for Medicare & Medicaid Services (CMS) issued a National Coverage Decision (NCD) and a product-specific HCPCS Q-code for Provenge in the US. The Q-code may facilitate the filing of Provenge claims and payment for reimbursement.[82] As described above, marketing authorisation was granted on April 29, 2010. This results in a time to reimbursement of 14 months.

8.4.2. Canada

Time to approval

Prochymal is currently the only advanced therapy in Canada.[58] Table 8.3 provides a more detailed overview regarding the time to approval for Prochymal. The clinical trials were conducted between 2005 and 2009. On March 12, 2010, a priority status review has been requested by the developer (Osiris Therapeutics), which was granted on April 30, 2010. Health Canada issued a Notice of Non-Compliance outlining various deficiencies with the submission. In addition to this, a non-withdrawal was issued by Health Canada on June 30, 2011 because the data submitted 'did not provide adequate support for approval of the proposed expansion of indications for the drug'.[83] On September 15, 2011, the developer filed a New Drug Submission (NDS) and conditional approval was granted on May 17, 2012. The time to approval for Prochymal is therefore 7 years.

Time to reimbursement

In Canada it is possible to apply for reimbursement at the national (federal) level.[7*] This can be done before full market authorisation.

Prochymal is currently not reimbursed in Canada because the developer has not yet applied for reimbursement.[58]

8.4.3. Japan

Time to approval

Table 8.4 provides a detailed overview of the time to approval and time to commercialisation of the two selected products JACC and HeartSheet. The developer of JACC (J-TEC) submitted the first clinical trial application to the Japanese Ministry of Health, Labour and Welfare (MHLW) in September 2001. It was approved by the MHLW in February 2004. In addition to this, J-TEC submitted a clinical trial protocol to the MHLW in April 2004. Eventually, the clinical trial completion notification was submitted to the MHWL in March 2007. After several years of conducting clinical trials,

[7*] Interview with an association and researcher in the field of advanced therapies (Canada).

J-TEC submitted an application for marketing authorisation on August 24, 2009. On July 27, 2012, JACC was officially granted marketing authorisation. The time to approval for JACC is therefore almost 11 years. After marketing authorisation, J-TEC started a clinical trial of all patients using JACE[84] and JACC[85] to prove that the products are safe to use and does not have any severe side effects.

The other product that was selected for this study is HeartSheet. The first clinical trial for HeartSheet started in 2007. The total clinical trial period for HeartSheet took around 7 years as the clinical trial was completed in 2014. After the clinical trial period, the developer (Terumo) applied for marketing authorisation. In 2015 the therapy was granted conditional approval, which means that the total time to approval for this product was 8 years.

Time to reimbursement

In Japan, currently 4 products are authorised for commercialisation. Of these 4 products, 3 products are reimbursed (JACE, JACC and TEMCELL). Only HeartSheet is not reimbursed, but is expected to be reimbursed in 2016 (see Annex 6, Table A6.2).

After the marketing authorisation of JACC on July 27, 2012 it was reimbursed via health insurance on April 1, 2013. The time to reimbursement for JACC is therefore 8 months.

HeartSheet was granted conditional approval in 2015. Conditional reimbursement requires up to 30% co-payment from Japanese patients depending on age and type of condition (see section 8.5.3). The time to reimbursement for HeartSheet is unknown, but will be around 1 year if it is reimbursed in 2016.

JACE is reimbursed under conditions. Criteria with regard to medical facilities and a clear and detailed patient record must first be met before the advanced therapy will be fully reimbursed.[86] It took 1,5 year before JACE was reimbursed, as the Japan Medical Association's Questionable Interpretation Committee was not convinced about the evidence concerning the safety and the effectiveness of the product, because it was tested on only two persons.

8.4.4. South Korea

Time to approval

There is not much information available about the average time to approval and time to commercialisation of advanced therapies in South Korea. Table 8.5 provides information on the timeline of the selected products.

In the case of Kaloderm, the developer (Tegoscience) was selected as best research project in 2001, and received NDA approval in 2003. Therafter, clinical trials regarding efficacy were conducted and Kaloderm was granted marketing authorisation in April 2005. Based on the available resources, this results in a total time to approval of around 4 years.

Time to reimbursement

In South Korea 18 products are granted marketing authorisation (see table A6-2) but not all of them are reimbursed. Of the 18 products, we found that 4 products are currently reimbursed (Cupistem, Queencell, Kaloderm and Chondron), 9 products are not reimbursed (Cartistem, HeartiCellgram, Neuronata-R, Cureskin, RMS Ossron, Immuncell-LC, CreaVax-RCC, Keraheal and Holoderm), and the reimbursement status

of the remaining 5 products (LSK Autograft, Autostem, Hyalgraft-3D, NKM and Adipocel) is not reported.

In April 2007, Kaloderm was approved for reimbursement by the National Health Insurance Service (NHIS). The total time to reimbursement for Kaloderm is therefore exactly 2 years.

Table 8.2 US

Date	Activity	Source
PROVENGE, AUTOLOGOUS CELLULAR IMMUNO-THERAPY (SIPULEUCEL-T)		
1996 – 2006	Start clinical trials and submitting IND	Yano (Kazuo) et al. 2015. Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan
2006	Submitting pre-marketing approval	Yano (Kazuo) et al. 2015. Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan
29 April 2010	Approval to manufacture/sell	Yano (Kazuo) et al. 2015. Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan
2011	Covered by insurance (price)	http://www.dendreononcall.com/reimbursement-resources.aspx
THERACYS, BACILLUS CALMETTE-GUERIN (BCG INTRAVESICAL LIVE)		
N/R	Application for manufacturing and sales	
8 November 2012	Approval to manufacture/sell	http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm327940.htm http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm310363.htm
N/R	Covered by insurance (price)	https://www.accc-cancer.org/publications/pdf/Patient-Assistance-Guide-2015.pdf

Table 8.3 Canada

Date	Activity	Source
PROCHYMAL, REMESTEMCEL-L, ADULT HUMAN MESENCHYMAL STEM CELLS (HMSCS)		
Feb 2005-2009	Start date clinical trials (260-261, 265, 270, 275, 276 and 280)	Clinicaltrials.gov
12 March 2010	Clinical assessment package requesting Priority Review status	Summary Basis of Decision (SBD) for PROCHYMAL® http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2012_prochymal_150026-eng.php
30 April 2010	Priority Review status was granted	Summary Basis of Decision (SBD) for PROCHYMAL®
12 January 2011	Health Canada issued a Notice of Non-Compliance (NON), outlining various deficiencies with the submission, including chemistry and manufacturing.	Summary Basis of Decision (SBD) for PROCHYMAL®
30 June 2011	Health Canada issued a NON-Withdrawal (NON/W) on the basis of outstanding issues related to clinical data	Summary Basis of Decision (SBD) for PROCHYMAL®
15 September 2011	Osiris re-filed the New Drug Submission (NDS)	Summary Basis of Decision (SBD) for PROCHYMAL®
17 May 2012	Conditional approval	Summary Basis of Decision (SBD) for PROCHYMAL®
2016	Full approval. The company has until 2016 to submit an application for full marketing authorisation.	Interview with a representative from body for reimbursement/pricing of medicines (Canada)
N/A	No reimbursement. Until now, the company has not yet applied for reimbursement.	Sowmya Viswanathan & Tania Bubela. 2015. Current practices and reform proposals for the regulation of advanced medicinal products in Canada. Regen. Med. 10(5), 647–663)

Table 8.4 Japan

Date	Activity	Source
JACC, HUMAN AUTOLOGOUS TISSUE FOR TRANSPLANTATION, AUTOLOGOUS CULTURED CARTILAGE		
September 2001	Clinical trial application submitted to MHLW	Press releases J-TEC http://www.jpte.co.jp/english/news/
February 2004	Clinical trial application approved by MHLW	Press releases J-TEC http://www.jpte.co.jp/english/news/
April 2004	Clinical trial protocol submitted to MHLW	Press releases J-TEC http://www.jpte.co.jp/english/news/
March 2007	Clinical trial completion notification submitted to MHLW	Press releases J-TEC http://www.jpte.co.jp/english/news/
August 24, 2009	Application for manufacturing and sales	Press releases J-TEC http://www.jpte.co.jp/english/news/
July 27, 2012	Approval to Manufacture and Sell	Press releases J-TEC http://www.jpte.co.jp/english/news/
April 1, 2013	Covered by insurance (2.08 million yen)	Press releases J-TEC http://www.jpte.co.jp/english/news/
HEARTSHEET, AUTOLOGOUS SKELETAL MYOBLAST SHEETS		
2002	Engaging in R&D activities for cardiac regenerative technology	Press release Terumo http://www.terumo.com/about/pressrelease/2012/008.html
2007	Developed myoblast sheets were sent to the PMDA + start clinical trials	Press releases Terumo and interview with a developer (Japan) http://www.terumo.com/about/pressrelease/2015/20150902.html
2012	A clinical trial at three medical institutions	Press releases Terumo http://www.terumo.com/about/pressrelease/2015/20150902.html
2014	Completed the study	Press releases Terumo http://www.terumo.com/about/pressrelease/2015/20150902.html
30 October 2014	Approval to produce and market its skeletal myoblast sheets as a regenerative medicinal therapy for treating severe heart failure caused by chronic ischemic heart disease	Press releases Terumo http://www.terumo.com/about/pressrelease/2014/20141031.pdf
2 September 2015	Conditional approval	Press releases Terumo http://www.terumo.com/about/pressrelease/2015/20150902.html
2016	Reimbursement (all products with (conditional) approval	Interview with a developer (Japan)
2020 (estimation)	Full approval within 7 years (5+2, because the limited target population)	Interview with a developer (Japan)

Table 8.5 South Korea

Date	Activity	Source
CUPISTEM, AUTOLOGOUS MSC PRODUCT		
N/R	Clinical trial Phase, full clinical trial data to support the approval have not been released (source published in March 2013); there is still no information available about the full clinical trial data	http://www.stempeutics.com/pdf/stem-cell-therapy-market.pdf
N/R	Application for manufacturing and sales	
January 2012	Approval to manufacture/sell	http://www.stempeutics.com/pdf/stem-cell-therapy-market.pdf
N/R	Covered by insurance (price)	
KALODERM, CULTURED EPIDERMAL ALLOGENEIC GRAFT		
November 2001	Selected as best new material research project by ministry of Commerce, Industry and Energy	http://www.tegoscience.com/english/tego/history.php
2003	In 2003 NDA approved, clinical trial conducted with regard to efficacy (clinical study on Kaloderm applied in patients with deep second degree burn)	http://idnps.com/basics/regenerative-surgery/15-2-cell-therapy-with-human-allogeneic-keratinocytes/
N/R	Application for manufacturing and sales	
April 2005	Approval to manufacture/sell (deep burn)	http://www.tegoscience.com/english/tego/history.php
April 2007	Approved for reimbursements by National Health Insurance	http://www.tegoscience.com/english/tego/history.php
February 2012	Post Marketing Surveillance approved	http://www.tegoscience.com/english/tego/history.php

8.5. Pricing and reimbursement

A quick scan of pricing and reimbursement and policies was performed using desk research and interviews with relevant stakeholders in the selected jurisdictions (see Annex 1 and Annex 9 for more information). The overviews provided below have been verified by the relevant stakeholders in each jurisdiction.

8.5.1. United States

In the US many actors are involved in the health care sector, including providers, insurers, employers, and the government. As most other high-income countries, there are both private and public insurers in the US health care system. The US government has almost no direct control outside of the federal Medicare and Medicaid programmes. With regard to health care expenditure, the US is by far the most expensive health care system in the world.

In 2010, a major reform took place by introducing the Patient Protection and Affordable Care Act (ACA - Obamacare). The main focus of this law is to provide "more Americans with access to affordable health insurance, improving the quality of health care and health insurance, regulating the health insurance industry, and reducing health care spending".[87]

The organisation and delivery of health care is a reflection of the free market system. The delivery system is loosely structured. The huge public and private investment in basic medical research and pharmaceutical development are often cited as an important driver of this "technological arms race".[88]

The US is one of the few countries in the industrialised world that does not regulate pharmaceutical prices.[89] The private sector is determined by negotiations between manufacturers and pharmacy benefit managers (PBMs) and insurers as part of the formulary listing process. Other pricing systems are used by the publicly funded organisations - Medicare and Medicaid. Congress sets the payment formulas for drugs under traditional Medicare, and the federal courts have ruled that Medicare cannot use a "least costly alternative" payment computation for these drugs (*Hays v Sebelius, US Court of Appeals, Washington DC, December 2009*). For example:

- Medicare part A (Hospital Insurance) covers inpatient drugs, along with all other inpatient costs in a single bundled payment diagnosis-related group (DRG), e.g. hospital care, nursing, home health and hospice care;
- Medicare part B (Medical Insurance) covers most drugs that are dispensed in physicians' offices and other services among others preventive care, laboratory tests, x-rays, mental health care and ambulance care;
- Medicare Part C is not a separate benefit; it is the part of Medicare that allows private health insurance companies such as HMOs and PPOs to provide Medicare benefits in the form of a Medicare Advantage plan;
- Medicare Part D (outpatient Prescription Drug Insurance) is the part of Medicare that provides outpatient prescription drug coverage. Retail pharmacy and mail order pharmacy dispense self-administered drugs and are reimbursed on a fee-for-service basis by a private insurer's pharmacy benefit that have contracts with the government.[90,91]

As stated above, the US depends highly on competition between payers with regard to pricing and reimbursing of health care services. This means that anything from

discounts, mark-ups for wholesalers & retail and final prices are effectively determined and restricted by competition on the market.

In pharmacy-dispensed drugs, private health plans use PBMs to manage drugs. In Medicare (part D), prescription drug plans (PDPs) have the same role. They have common strategies. In contrast to several European countries, the private and public payers in the US try to influence prices by using tiered formularies. In an earlier scheme, consumers paid the same rate for any drug. Now, with different tiers, payers charge different amounts for different drugs. This means that the amount of (co)payment is dependent in which tiered formulary the pharmaceutical is placed. Usually, the lowest tiers are meant for (cheaper) generic drugs. The second tier includes preferred on-patent brands, with co-payments between US$25–45. The third tier consists of non-preferred brands and therefore has a higher co-payment, between US$45–90 per month. The fourth and highest tier is used for specialty drugs, the co-payment rates are between 25–30% of the list price.[92]

The goal of using four formularies with different levels of cost sharing and prior authorisations is to enable PBMs and PDPs in steering drug utilization towards the preferred drugs. This system provides leverage in negotiations with manufacturers. This entails discounts on price, for which in return, a preferred formulary position is acquired. A healthcare plan could restrict the amount of preferred providers, so that manufacturers are willing to offer higher discount and rebates for instance. Unlike the Medicare Part D and C - operated by private sector entities - the Medicaid programme uses mandatory rebates for manufacturers of pharmaceuticals.[90]

Physician-dispensed drugs (Medicare part B), reimburses dispensing physicians at the manufacturer's Average Selling Price (ASP) plus a six percent margin.[90]

Hospital inpatient drugs are dispensed via an inpatient setting. Reimbursements (Medicare part A) of these pharmaceuticals are arranged via DRG payments, which include wages of the staff, pharmaceutical products, costs of the building etc. National average costs are leading for Medicare to adjust the DRG payment rates over time. Private payers negotiate various forms of bundled payment for inpatient hospital care, with private rates generally above Medicare rates.[90]

In specialty drugs, the system of tiered formularies has less of an impact. In contrast to generics, highly specialized medicines have naturally very few substitutes. Therefore, pharmaceuticals to treat complex, rare and life-threatening diseases remain relatively high-priced. For such pharmaceuticals, the PBMs have very limited measures to control high spending. Those options remain high patient cost-sharing and/or prior authorisations to steer the patient to cheaper alternatives. Because these methods only limit the utilization to a certain drug and not the price of the pharmaceuticals, there is no effect on the list price that the manufacturer sets. Both Medicare's PDPs and private PBMs place specialty[8]* in the fourth tier (25–30% co-payment). In theory, cost sharing could cost patients up to hundreds of dollars per month. In practise, such high numbers of cost sharing are not the case. Consumers could sign up for supplementary insurance coverage or join patient assistance programs (PAPs) that will cover the excessive costs of specialty drugs.[92]

There is not a clear legal framework with regard to pricing and reimbursement of advanced therapies. The labelling of a product is controlled by the FDA. The FDA (marketing authorisation) uses different classifications than Medicare

[8]* Medicare defines a drug as 'specialty' when it costs US$600 or more a month.

(reimbursement). The two entities have different laws that govern their activities and are supervised by different committees of Congress. Categorizing these products for reimbursement (according to the classification used in the regulation) is therefore difficult; this might raise questions about determining the most appropriate payment for certain products. An example is autologous immunotherapy for prostate cancer, Sipuleucel-T (marketed as Provenge); when it first entered the market, there were questions regarding whether Medicare would make payment as a vaccine, a transplant, or under the traditional drug benefit. Under the Medicare statute, written by Congress, traditional Medicare is not generally allowed to pay for vaccines – with exceptions for pneumococcal, hepatitis B, and influenza vaccines.

In the US, conditional reimbursement of drugs can exist. The Centres for Medicare and Medicaid Services (CMS) are engaged with coverage mechanism linked to the collection of additional evidence to inform subsequent reviews of coverage decisions.[93] For example, one interviewee mentioned that Medicare has about 20 diagnostic and therapeutic technologies that are subjected to conditional coverage in the context of a clinical study.

8.5.2. Canada

Healthcare for Canadians is publicly funded through a tax-based system. All Canadians and residents have free access to services, (medical) procedures and medicinal products in hospitals.

Reimbursement of drugs in Canada is arranged through a mixture of parties. From the government, this is arranged by federal, provincial and territorial bodies; private insurers provide reimbursement as well; lastly there are out of pocket payments by medical consumers.

About one third of the Canadian's are covered by governmental bodies through publicly financed programmes like Medicare, a universal and publicly funded programme.[94] Recipients of these programmes will be required to pay some portion of the cost of most drugs. Some of those programmes target specific populations like social assistance beneficiaries or seniors for instance. Where drugs administered in a hospital are covered through Medicare, outpatient drugs are not reimbursed by this programme. In Canada the latter is predominant, with 66% of the people who obtain drugs by means of private insurers. Most people have private insurance through employer group insurance or are insured via relatives. In private plans, medical consumers could pay directly or partially for their medication due to co-payments or a deductible.[95] Private plans though, are more extensive than public ones in terms of their formularies. Provincial and territorial governments are responsible for the decision about inclusion of new medicinal products based on recommendations issued by the Canadian Agency for Drugs and Technologies in Health (CADTH), Canadian Expert Drug Advisory Committee or the pan-Canadian Expert Review Committee, for cancer drugs. These recommendations consider clinical and cost effectiveness and patient impact. Public drug plans will also consider specific budget impacts. On that basis, they come to a reimbursement decision and have the possibility to negotiate the price of the medicinal product with the manufacturer. Those plans are mainly directed for those whom drug costs form are a high financial burden.[96]

Canadian hospitals work with fixed budgets and / or fee-for-service. The budgets are determined on historical budgets, inflation and politics.[97] The provincial governments are responsible for determining the global hospital budgets through their Ministries of Health. From these budgets, hospitals buy pharmaceuticals for inpatient use, which are publicly, and 100% covered by the Canada Health Act. To make use of economies of scale, hospitals mostly use group-purchasing programmes, which establish group

contracts for set prices - hospitals then buy directly from the manufacturer at the contract price.[97,98,99]

The federal government has a responsibility regarding the pharmaceutical sector on two main areas: approval of pharmaceutical products based on safety and efficacy assessments; and the management of pharmaceuticals through federal price regulation of the Patented Medicines Pricing Review Bureau (PMPRB). Pricing of patented pharmaceuticals is regulated by the federal government, whether the medicinal product is covered or not. The body responsible for this is the PMPRB. This is an independent body, which mandate can provide sanctions and enforce reductions on price of patented medicines. For every medicinal product a maximum ex-factory price is set, to protect medical consumers from excessive prices. Non-patented drugs are not regulated by the PMPRB.[95] In its consideration, the PMPRB reviews the therapeutic value of the product and critically observes prices of existing medicines in Canada and uses the prices of medicines in other countries as a reference point. The PMPRB has a mandate to protect Canadian healthcare consumers from excessive prices of patented pharmaceuticals sold in Canada; prices of off-patent original products are not regulated in Canada.[98]

Prices for generic drugs are relatively high compared to other countries as there is a lack of competition in a highly concentrated market. For patented drugs, the prices are considered to comparable to other industrialised countries. This is due to the fact that the provinces have purchasing power and the PMPRB regulates a ceiling price.[98]

To determine a maximum price, the Human Drug Advisory Panel (HDAP) of the PMPRB plays a central role. This panel has the task to perform a scientific review of new pharmaceutical products within the PMPRB. HDAP classifies products in four categories with regard to the (added) therapeutic value:[96]

- Breakthrough drug;
- Substantial improvement;
- Moderate improvement;
- Slight or no improvement.

As mentioned before, the PMPRB has the task to regulate ex-factory prices for patented drugs that are on the market in Canada. External reference pricing (ERP) was adopted in 1987 as part of the price regulation process. This is used for pricing of innovative medicines. The PMPRB may use ERP for products above category 4 (‘slight or no improvement’). In ERP, the median of the ex-factory prices of the same-patented drug with the same strength and dosage form in seven countries is used. The countries are: France, Germany, Italy, Sweden, Switzerland, United Kingdom (UK) and the US. These countries were selected based of their economic and geographic similarities to Canada. In addition, they share the same values with Canada: that the amount of research and innovation of the pharmaceutical product determines the ‘maximum average potential price’ for a new-patented drug.[100] In case the reviewed drug is sold in an even number of countries, the median is determined as the average of the middle two country prices. If the drug is sold in fewer than five countries when it enters the market in Canada, the median international price is calculated on an interim basis, the PMBRB re-determines this price after three years.[101] There is an exception when the ERP does not determine the price ceiling. This occurs when there are similar drugs with comparable dosage of the same medicine and patentee, which are sold in Canada as well. The comparison test is then focussed on Canadian products when determining the ceiling price for the new product. However, provinces may

negotiate lower prices with the manufacturer when they feel the price is too high. These negotiations and eventual agreements are private and not announced in the public domain.[101]

When a manufacturer wants to be reimbursed in a public drug scheme, it has to submit the product dossier to the Common Drug Review (CDR), or when it involves cancer drugs, to the Pan-Canadian Oncology Drug Review (pCODR). Both review processes are part of the CADTH. This agency provides recommendations for reimbursement to the drug plans in Canada (except Quebec). It does this on the basis of an evaluation of the clinical effectiveness and cost-effectiveness of approved drugs, including advanced therapies. For advanced therapies, however, it is not needed that full marketing authorisation has been obtained in order to seek reimbursement. In Canada, Prochymal was approved under the conditional approval procedure in 2012 (and the company has until 2016 to submit an application for full marketing authorisation). Until now, the company has not yet applied for reimbursement.[58]

In Canada, there are several incentives to improve the chance of reimbursement by collecting relevant evidence on the medicinal product or technology. One of the most important programmes is the MaRS EXCITE programme (see section 8.3.2).[62] In addition, the EXCITE programme could also facilitate access to global markets as Ontario's approach to evidence-based validation is highly regarded across Canada and abroad.[102]

8.5.3. Japan

The healthcare system in Japan is characterised by universal access to care and a comprehensive benefits package for all health services (National Health Insurance - NHI). The Japanese public health system is regulated to the level of local governments (prefectures); and co-insurance exists 30% for curative health services and 10% for long-term care services.[103]

The Japanese healthcare system underwent several health care reforms in the last two decades. Since 2000, reforms were implemented to manage rising health care cost. In 2012 cost containment measures have been implemented, such as price cuts of long-standing drugs and the promotion of generics uptake (compared to EU and US, this uptake is relatively low).[104] This has to be achieved without affecting the sustainability of the pharmaceutical industry and access to (innovative) therapeutic treatments.[105,106]

Reimbursement of medicinal products/medical devices and regenerative medicine in general can only be achieved when the product is (conditional) approved. The review of a product is carried out by the Pharmaceutical and Medical Devices Agency (PMDA). After approval, a manufacturer who wants its product to be reimbursed, has to apply for the NHI. The application is discussed in a hearing of the Health Policy Bureau (HPB), part of the MHLW. The main objective during the hearing is to assess the evidence on quality and effectiveness of the product. Eventually a price for the product based on expert opinions and the evidence provided is examined and decided at the Central Social Insurance Medical Council (CSIMC). The manufacturer may appeal once against this proposal. After the process of approval and price setting, a product will enter the NHI drug price list. The CSIMC has two methods for setting the price of new pharmaceutical products; cost calculation and similar efficiency.[106] The first method is used when no comparator is available on the Japanese market and is calculated as the sum of essential costs in drug production of this particular drug. The costs included are materials, labour, manufacturing, marketing, distribution, taxes and an operating profit when innovation is shown. A product without any competitors cannot charge a higher price through a premium.[106]

When a pharmaceutical product has a comparator, the pricing will be linked to characteristics of the comparator's product. Several of these characteristics are then compared, such as: innovation, usefulness, marketability, paediatric use etc. On top of the cost calculation method, a premium could be awarded when a pharmaceutical product can demonstrate significant benefits in comparison with alternative competitor products. Premiums are designed by the government as an incentive for innovation within the pharmaceutical industry. Benchmark criteria are set by the governments on which the pharmaceutical product will be evaluated in order to determine the premium percentage.[106]

Both pharmaceuticals with and without comparators can receive price adjustments based on average foreign prices - reference prices of France, Germany, the UK and the US are used. For example, an upward adjustment when the estimated price is below 75% of the average foreign price. A downwards adjustment will be made when the estimated price is 125% above the average foreign price. This is applicable to all pharmaceutical products.[106]

If the product is approved as a new category product (e.g. regenerative medicine), then the HPB decides appointment of specific pricing expert committee of CSMIC to take charge (i.e. drug pricing or medical materials pricing) by looking at the major mode of action (i.e., is it a drug or medical device). This is because a new category product pricing committee is not yet established at CSIMC. Currently, the committee is applying an orphan drug pricing or cost assessment approach in which standard cost parameters are still different between drug and medical materials. The orphan drug pricing scheme depends on the cumulative (actual) cost price, divided by the number of target patients. The patient range is small, therefore the MHLW and CSIMC will estimate what the acceptable sales marketing profitability or what the marketing costs by comparing with its standard ratio for the same product categories. The MHLW is considering defining the pricing methodology for regenerative medicine, the procedure will remain the same. There is an understanding to use real cost data – i.e. cost accounting system – for regenerative medicine. For example, Heart Sheet is split into two parts. The first part, kit A, is to get the tissue from hospital to company and isolate cells and keep frozen, the second kit, the B kit, is used to bring cells from company storage to hospital and culture it to form cell sheet at the hospital. The hospital sends tissues to company by using kit A and receives frozen cells from the company by using kit B. Then the hospital processes it for the surgery. If the patient dies before the surgery, kit B does not have to be purchased.[9]*

As is the case in Canada, for advanced therapies it is not needed that full marketing authorisation has been obtained in order to seek reimbursement. In addition, therapies that receive conditional approval (Heart Sheet) are eligible for reimbursement but this requires up to 30% co-payment from Japanese patients depending on age and type of condition.[93]

From a pricing point of view, the Heart Sheet product is relatively expensive. Reimbursement price of Kit A is Yen 6.36mm and Kit B for each cell sheet costs Yen 1.68mm. Standard usage of this product requires five sheets, therefore the total reimbursement price will be approx. 130.000 US$ dollar (115.000 euro) per treated patient.

The first approved product JACE is priced per 'sheet' as medical device. This means that if you need 20 sheets to treat a patient, the price has to be multiplied by 20.

[9]* Interview with an expert in the field of regenerative medicine (Japan).

Insurance, however, has limited the amount of sheets to be used during a procedure. Regulatory condition, however, on the other hand, is used for only heavily burned patients and a doctor often needs 30-40 sheets to cover the entire body. Therefore, the insurance coverage ceiling number has been increased after its initial approval. For the second product (JACC), the physician normally needs about four-five units. Reimbursement is set on one price as medical device, regardless on how many units are used. This is about 20.000 US$ dollar (17.600 euro).[10]*

8.5.4. South Korea

The South Korean health care system is universal, and health care insurance is compulsory.[107] In 1977, the first social insurance programme was launched under the Korean National Health Insurance (KNHI), which is governed by the Ministry of Health and Welfare. Although access to healthcare in South Korea is unrestricted, treatment is not completely free. Funding of the KNHI is arranged through numerous sources, including premium payments, taxes, an employment funds and a relatively high share of co-payments. The rate of reimbursement for covered services is 80% for inpatient care and 50-70% for outpatient care. For pharmaceutical products, about 70% is reimbursed. In 2000, the South Korean healthcare financing was reformed. One of the changes was the merger of health insurance societies into the National Health Insurance Corporation (NHIC, now called National Health Insurance Service - NHIS) as the single payer for health care services. This was done in order to improve equality and efficiency.

In 2007, a Positive List system regarding pharmaceutical products was introduced in Korea. Before 2007, pharmaceutical products that were approved by the Korea Food and Drug Administration (KFDA, now the Ministry of Food and Drug Safety) were also reimbursed. The results was an extensive list of reimbursable drugs - over 20.000 products - for new pharmaceutical products, cost-effectiveness and budget impact were not taken into account in reimbursement decisions.[108] In light of rising health care costs, both new pharmaceutical products and medical technologies now need to demonstrate value for money in order to be approved and reimbursed.[107] South Korea introduced economic evaluations for drug reimbursement decisions, as the first Asian country, by introducing health technology assessment (HTA) – based on international models from countries such as the UK and Canada.[109] In 2008, the National Evidence-based healthcare Collaborating Agency (NECA) was established to provide information about medical devices, medicines, and health technology through objective analysis of evidence through comparative assessment of health technologies. NECA was established as HTA agency by the Korean government as an independent agency collaborating with the Korean Ministry of Health and Welfare.[110]

The reimbursement process and the price negotiations of pharmaceutical products in Korea are separated. The specialized governmental Drug Benefit Coverage Assessment Committee (DBCAC), remitted to the Health Insurance Review and Assessment service (HIRA) is responsible for the reimbursement process of pharmaceuticals after a manufacturer submits an application for a new drug. In its review, HIRA first compares the new drug with existing alternatives and reviews the pharmacovigilance and the claims of the manufacturer on the product. The main criteria in the decision-making process regarding reimbursement are (proven) clinical benefit, cost-effectiveness, the overall impact on health-care budget, the reimbursement status, (reference) prices in other countries and potential public health impacts.[109] Some exceptions for approval can be made when no alternative treatments are available for severe-, rare- or life-threatening diseases.

[10]* Interview with an expert in the field of regenerative medicine (Japan).

The results of the review by HIRA are distributed to the NHIS and provider institutions. HIRA also (re)evaluate the clinical benefits and price(s) of pharmaceutical products that were approved before the Positive List System was introduced (i.e. 2006).[107,108] When approval is given, the NHIS is responsible for price negotiations with the manufacturer. Several factors are taken into account when these negotiations take place, such as price-volume considerations. The aim of the single insurer policy in Korea is to control pharmaceutical prices. Countries such as France, Germany, Italy, Japan, Switzerland, the UK and the US are used by the South Korean government as reference countries. In addition, three year evaluations of pharmaceutical products are used to reconsider prices. If a pharmaceutical company wants a higher price (in relation to the best comparator) for a new pharmaceutical product, a cost-effectiveness or cost-utility study on the product has to be presented. The decision by HIRA will be based solely on the incremental cost-effectiveness ratio (ICER). Since HIRA does not hold on to a pre-determined ICER threshold, it will be accepted or rejected with regard to disease severity, societal burden, quality of life, and innovativeness.[108,109]

Generic pricing has a different structure than for branded products. When the patent of a pharmaceutical drug expires, a generic automatically has a 20% reduction in price. Next to that, the first five generic products for a specific disease receive 85% of the reduced originator price. From the sixth generic product on, manufacturers receive 90% of the generic that is priced lowest. From early 2012, changes were implemented with regard to generic pricing. The first year after a patent expired, generics are capped at 59.5% of the originator price. In the second year after patent expiry, the maximum price is 53.5% of the originator.[107,110]

8.6. References

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9. Conclusions

The objective of this study was to provide comprehensive and factual information about the US, Canada, Japan and South Korea with regard to:

- advanced therapies that are already available to patients;
- those that are in development phase; and
- the regulatory frameworks governing advanced therapies in these four jurisdictions.

The definition used in this report for advanced therapies is provided in Section 1.1.1. and is similar to the definition for Advanced Therapy Medicinal Products in the EU.

At the data lock point of this study (31 December 2014), we identified 132 ongoing research projects on advanced therapies and 5 approved advanced therapies in the US. In Canada, 39 research projects were ongoing and one advanced therapy was approved. 131 research projects on advanced therapies were conducted in Japan, while two advanced therapies were approved. In South Korea we listed 43 ongoing research projects on advanced therapies and 18 approved advanced therapies. We discovered that not all approved advanced therapies are reimbursed (or it is not known).

We found two different ways in which advanced therapies are currently regulated in the different jurisdictions. In Canada, US and South Korea most advanced therapies are formally regulated as medicinal products (biologics), albeit consideration is given to the specific characteristics of advanced therapies in individual decision making procedures for marketing authorisation - often in close consultation with developers. Given that the regulatory frameworks in these three jurisdictions are largely similar, differences in research activities between these jurisdictions are not likely to be a direct outcome of differences in the regulatory frameworks, and more likely to stem from other characteristics of the innovation system for advanced therapies in each jurisdiction. Assessment of these characteristics was, however, beyond the scope of this study. In Japan, a specific regulatory framework for advanced therapies has recently been enacted. It is therefore difficult to measure the impact of this regulatory framework with regard to the field of advanced therapies.

Below, we highlight the main findings and conclusions per main part of the study (analysis of the regulatory frameworks governing advanced therapies, research activities and availability of advanced therapies and economic aspects of the advanced therapies market).

Analysis of the regulatory frameworks governing advanced therapies

We observed a number of differences between the four studied jurisdictions in how they incorporate the regulation of advanced therapies in their existing medicines regulatory framework. In the US, Canada and South Korea, advanced therapies are regulated as a subcategory of biologic drugs. In general, standards for biologic products apply. In these three jurisdictions, there was a common understanding that requirements for biologic products cannot be directly translated to the development trajectories of advanced therapies. Therefore, all authorities have issued guidance on how to interpret common standards for the development of advanced therapies. However, the number of guidelines available in each jurisdiction, their level of detail, the issues covered in the guidelines and the specific interpretations of the legal framework in the respective jurisdiction differ. In light of this variation, we summarize the main conclusions for each jurisdiction.

In contrast, Japan has introduced advanced therapy-specific legislation, which includes a separate marketing authorisation pathway which is only accessible to advanced therapies.

United States

In the US, advanced therapies are regulated as biologic products under the Food, Drug & Cosmetics Act and the Public Health Services Act. A common distinction is made between 351 gene-, cell- and tissue (GCT)-based products which require a marketing authorisation, and human cell, tissue and cellular and tissue-based products (HCT/Ps). The group of 351 GCT-based products is broader than the definition of advanced therapies. They include for example specific types of cell-based products that have a systemic effect. To interpret the exact requirements for authorisation, there are a number of 351 GCT-based product specific guidelines that cover manufacturing requirements for Investigational New Drug (IND) applications and guidance for preclinical assessment and design of early-phase clinical trials, among others. The Office for Cellular, Tissue and Gene Therapies oversees authorisation of clinical trials and marketing authorisation for 351 GCT-based products. Developers need to submit an IND application to gain clinical trial authorisation and a Biologics License Application to obtain a marketing authorisation after which authorisation is decided upon on a case-by-case basis. A main difference for 351 GCT-based products compared to other biologic products is that manufacturing and quality regulations for HCT/Ps are applicable as well, in addition to current Good Manufacturing Practice (cGMP) for biologic products. Patients can have access to investigational advanced therapies by participating in a clinical trial or through the Expanded Access programme. Except for various marketing authorisation pathways, there is no other regulatory pathway to gain access. In the post-marketing phase, advanced therapies are regulated as any other drug or biologic product.

Canada

Canadian federal regulation classifies advanced therapies as drugs that are regulated under the Food and Drugs Act. They fall within the subgroup of biologic drugs. A distinction is made between GCT-based products regulated as biologic drugs and cell or tissue therapies for transplantation (CTO therapies). The definitions used to regulate GCT-based products as biologic drugs is broader than the definition of advanced therapies. For example, cell-based products that only have a metabolic effect for its mode of action are included. CTO therapies do not meet the definition of advanced therapies. To interpret requirements for biologic drugs, one guideline document has recently been issued that provides information on how to prepare Clinical Trial Applications, specifically for cell-based products. Two centres within the Biologics and Genetic Therapies Directorate of Health Canada share responsibility for distribution of advanced therapies. Exact requirements for clinical trial and market authorisation of advanced therapies are largely decided upon on a case-by-case basis. A main difference between the regulation of biologic drugs and other drugs are product quality standards, which are also applicable to advanced therapies including the Lot Release Programme. Manufacturing and quality regulations for CTO therapies also apply to advanced therapies, in addition to GMP regulations for biologic drugs. Individual patients may be granted access to investigational advanced therapies outside of clinical trials through the Special Access Programme. Except for participation in clinical trials and various marketing authorisation pathways, there are no other regulatory pathways to gain access to advanced therapies. Post-marketing surveillance is similar for all drugs.

Japan

Since 2014 the Japanese legislation includes separate laws and regulations for regenerative medicine. The definition for regenerative medicine is slightly broader than for advanced therapies. For example, cell-based therapies can be included solely on the basis of more-than-minimal manipulation. There are two laws in place: the Act on the Safety of Regenerative Medicine (RM Act) covers academic research with regenerative medicine. The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act) covers clinical trials that are conducted to obtain marketing authorisation. The standards for application and conduct of clinical research under the RM Act and clinical trials under the PMD act differ:

- Under the RM Act, a risk-based approach is used to authorize clinical research. Standards similar to Good Clinical Practice (GCP) and Good, gene, Cellular and Tissue-based product manufacturing Practice (GCTP) are in place, but there are no external inspections, for example. Results of clinical research cannot be used for a marketing authorisation;
- Under the PMD Act, developers enter a more extensive regulatory pathway than under the RM Act which is expected to result in a marketing authorisation. Compliance with GCP, GCTP and Minimum Requirements of Biological Ingredients is mandatory. The approval pathway is accessible for regenerative medicine products only and enables a time-limited conditional approval of regenerative medicine based on quality, safety, and *probability* of efficacy data. After conditional approval, confirmatory data to indicate a positive benefit-risk profile needs to be collected and submitted for full marketing authorisation after approximately seven years. Additional safety and quality post-marketing measures are in place for conditionally approved products.

Access to regenerative medicine products is possible under various frameworks: patients can be treated with non-commercialised products and treated off-label with marketed products under the RM Act, patients can be treated with similar product as a marketed product under the RM Act, and the compassionate use programme under the PMD Act enables access to investigational products for patients that cannot enrol in clinical trials.

South Korea

Cell and gene therapy products are defined as subtypes of biologic products under the Pharmaceutical Affairs Act in South Korea. The applicable definition for cell therapy products does not fully correspond to the definition of advanced therapies. While, gene therapy products adhere to the definition of advanced therapies, cell-based products require marketing authorisation on the basis of physical, chemical and/or biological manipulation and processing within medical centres. Guidance is provided on how to interpret biologic product regulations for gene and cell therapy products. Guidance mainly covers a number of manufacturing and quality requirements. The Cell and Gene Therapy Products Division of the National Institute of Food and Drug Safety evaluates IND applications and New Drug Submissions of advanced therapies, which are authorized by the Ministry of Food and Drug Safety Headquarters. Compared to biologic products, quality requirements are different for advanced therapies. There are specific batch release control measures and site inspections. Access to investigational cell and gene therapy is possible through participation in clinical trials, compassionate use and marketing authorisation pathways. No specific post-marketing surveillance is in place for advanced therapies.

Overview of research activities and availability of advanced therapies

In the **US** we found 132 ongoing research projects on advanced therapies (10,6% phase II-III or III trials) and 5 approved advanced therapies. In October 2015, one

more product was approved by the FDA. In **Canada** 39 research projects were ongoing (15,4% phase II-III or III trials) and one advanced therapy is approved. In **Japan** 131 research projects on advanced therapies were underway (2,3% phase II-III or III trials) and two advanced therapies were approved. Since September 2015 there are two more products approved in Japan. In **South Korea** 43 ongoing research projects on advanced therapies (14% phase II-III or III trials) were listed and 18 approved advanced therapies. In **most jurisdictions** the majority of the developers involved in research projects are for non-for-profit organisations or academia (US: 74,2%, Japan: 92,4% and South Korea: 74,4%). In **Canada** the involvement of for profit and non-for-profit/academic organisations is more balanced (51,3% and 48,7%). With regard to the late phase trials, we found that in the **US and Canada** the majority of all late phase trials are done by for profit organisations (respectively 71,4% and 83,3%). In **Japan and South Korea**, however, we found that for profit organisations appear not to be involved in late phase trials. Although it has not been part of this study, the differences between jurisdictions may be due to differences in registration practices (e.g. in Japan the company responsible for the registration of a clinical trial is often a non-for profit or academic organisation, while in practice the product is developed in partnership with a for profit organisation) and/or the R&D environment. These hypotheses need be further tested.

Analysis of the economic aspects of the advanced therapies market

Relevant intellectual property rights legislation

In the **US,** substantially manipulated cells are patentable as long as a claim is not encompassing a human being. For example, the patent eligibility inventions with stem cells depends on the extent of human manipulation of the stem cells and how this can be translated into a meaningful claim for a patent. Whether substantially manipulated cells are patentable in **Canada** is dependent on the origin and the features of the substantially manipulated cell(s). For example, a somatic cell taken from an organism, and cultured outside the body (e.g. tissue engineering), is patentable. In **Japan** it is only possible to receive a patent when a product is material based (i.e. not for a method) – e.g. induced pluripotent stem cell (iPS). In **South Korea** substantially manipulated cells (e.g. stem-cell related inventions) are patentable according to the statutory requirements that apply to all types of patents.

Incentives to support developers of advanced therapies

In addition to IPR legislation, several other incentives exist to support developers of advanced therapies. The main mechanisms in **all jurisdictions** include trade secret protection, data protection, as well as funds and research networks to stimulate (clinical) research in the field of advanced therapies. Especially, the **US, Canada and Japan** stimulate partnerships between researchers and industry through networks. As described above, the jurisdictions have regulatory pathways in place to decrease the time to marketing authorisation.

Time to approval and reimbursement

The period from R&D to a reimbursed advanced therapy can be up to 20 years. The time to approval differs per type of advanced therapy (cell-, tissue or gene based therapy). Also, time to reimbursements differs between the jurisdictions. However, not all advanced therapies that have been granted marketing authorisation are also reimbursed. In the **US**, 3 out of 5 advanced therapies are reimbursed, the approved product in **Canada** is not reimbursed, in **Japan** all approved products are reimbursed and in **South Korea** 4 products are reimbursed, 9 are not reimbursed and the reimbursement status of the other products (5) is not known. The reasons for these divergent practices have not been assessed as part of this study, but may be due to

differences in pricing and reimbursement systems, as this is a competency of each jurisdiction. This claim, however, would need to be further investigated.

Annexes

Annex 1. Overview of interviews with stakeholders

Table A1.1 Overview of interviews with stakeholders

Country	Type of organisation
Canada	Competent Authority
Canada	Association & investigator
Canada	Developer (academic)
Canada	Developer (academic)
Canada	Developer (academic)
Canada	Body responsible for reimbursement/pricing of medicines
Canada	Expert in the field of intellectual property
Canada	Patent office
Japan	Competent Authority
Japan	Association
Japan	Association
Japan	Competent Authority
Japan	Developer (industry)
Japan	Developer (industry)
Japan	Developer (academic)
Japan	Investigator (academic)
Japan	Developer (academic) / Association
Japan	Patent office
Korea	Competent Authority
Korea	Association
Korea	Association
Korea / US	Developer (industry)
Korea	Independent agency collaborating with the Ministry of Health and Welfare
US	Association
US	Developer (industry)
US	Developer (academic)
US	Developer (non-for-profit)
US	Developer (industry)
US / Canada	Innovation attaches
US	Developer (industry)
US	Association
US	Developer (industry)
US	Developer (industry)
US	Body responsible for reimbursement/pricing of medicines
US	Expert in the field of intellectual property
US	Patent office
US	Association

Annex 2. Questionnaire used for exploratory and in-depth interviews

The objective of the interviews was twofold: (1) obtain factual information about the regulatory framework (2) provide insight in views and perceptions of stakeholders on the functioning of this framework.

The semi-structured interviews consisted of the following five main topics:

- General regulatory framework;
- Approval procedures for advanced therapies including post-marketing requirements;
- Clinical trials for advanced therapies;
- Quality and manufacturing of advanced therapies;
- Financial incentives for R&D for advanced therapies.

Specific questions on these topics were tailored to each jurisdiction, the background of the interviewed stakeholder and knowledge gaps of the researchers on the regulatory framework.

Views and perceptions that were discussed in all interviews were:

- General factors of the national innovation system of the jurisdiction that facilitates or hinders research, development and approval of advanced therapies;
- Specific factors of the regulatory framework of the jurisdiction that facilitates or hinders research, development and approval of advanced therapies;
- Opinion on the number of approved advanced therapies;
- Opinion on the reimbursement system for advanced therapies.

The semi-structured nature of the interviews also provided room for further discussion in case answers of the interviewees prompted additional questions.

The interviews were conducted by telephone after detailed reading of relevant background material (e.g. company profile, public assessment reports of registered products, local regulatory documents, etc.).

Annex 3. Full search strategy and inclusion criteria to provide an overview of research activities and availability of advanced therapies

Literature and desk research

The issues that were addressed through literature and desk research focused on:

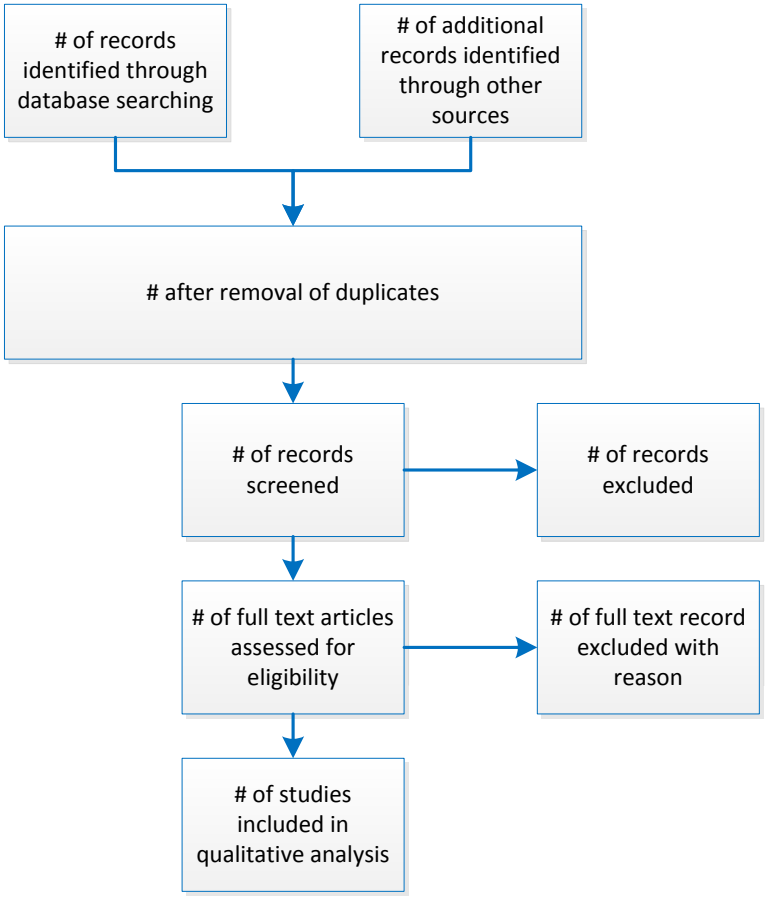
a) Data about ongoing research projects;
b) Information about advanced therapies available to patients;
c) Information about the size of the developers involved in activities under a) and b) and analysis of the relative weight of academia and non-for-profit sector.

The literature search involved the following steps:

1. Selection of databases to be used;
2. Define inclusion and exclusion criteria;
3. Defining the search terms and set-up search protocol;
4. Scanning titles and abstracts to make first selection by two reviewers;
5. Light reading of first selection to make second selection;
6. Full reading of second selection to make final selection of literature to be included;
7. Adjust search terms if necessary and repeat the previous three steps;
8. Perform the review of the final selection of literature.

A schematic overview of our search strategy is presented in Figure A3.1 below.

Figure A3.1 Overview of search strategy



Published literature, notably publications reporting on-going research

With regard to published literature, we will systematically search the electronic databases PubMed, MEDLINE, EMBASE, International Pharmaceutical Abstracts and Web of Science to identify relevant journal articles, using the following inclusion criteria:

Publication

Scientific literature.

Type of studies

All types of studies (including RCT, controlled before and after study, case study, evaluation, (systematic) review).

Key search terms:

Advanced therapies:

- ATMP;
- Advanced therapies;
- Advanced therapy medicinal product;
- Regenerative medicine;
- Cell therapy;

- Cell-based product;
- Cell-based therapies;
- Gene therapy;
- Tissue engineering;
- Tissue engineered products;
- Authorised clinical trials.

Geographical zone

US, Canada, Japan, South Korea.

Date

January 1, 2008 to search date (between May / August 2015) in each country. We included studies that describe the situation in the respective country as it was on 31 December 2014 (data lock point).

Exclusion criteria

Advance therapies that include “cells/tissues that have only been subject to minimal manipulation used to maintain the same function in the same anatomical or histological environment in the recipient as in the donor” and “non-viable cells or tissue acting solely through mechanical means”.

Table A3.1 PubMed and EMBASE search

Database	Search string (including MeSH search terms)	#hits	Date	Database	Search string (including EMTREE search terms)	#hits	Date
PubMed/MeSH	("Cell- and Tissue-Based Therapy"[Mesh]) OR ("Tissue Engineering"[Mesh]) OR ("Regenerative Medicine"[Mesh]) OR ("Genetic Therapy"[Mesh])			EMBASE/EMTREE	regenerative medicine'/exp OR 'cell therapy'/exp OR 'gene therapy'/exp OR 'tissue engineering'/exp		
PubMEd/search terms, ti/ab	("ATMP"[Title/Abstract]) OR ("Advanced therapies"[Title/Abstract]) OR ("Advanced therapy medicinal product"[Title/Abstract]) OR ("Regenerative medicine"[Title/Abstract]) OR ("Cell therapy"[Title/Abstract]) OR ("Cell-based product"[Title/Abstract]) OR ("Cell-based therapies"[Title/Abstract]) OR ("Gene therapy"[Title/Abstract]) OR ("Tissue engineering"[Title/Abstract]) OR ("Tissue engineered products"[Title/Abstract])			EMBASE/search terms, ti/ab	atmp':ab,ti OR 'advanced therapies':ab,ti OR 'advanced therapy medicinal product':ab,ti OR 'regenerative medicine':ab,ti OR 'cell therapy':ab,ti OR 'cell-based product':ab,ti OR 'cell-based therapies':ab,ti OR 'gene therapy':ab,ti OR 'tissue engineering':ab,ti OR 'tissue engineered products':ab,ti		
PubMed Filters	Case Reports, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Comparative Study, Controlled Clinical Trial, Multicentre Study, Randomized Controlled Trial, Observational Study, Clinical Trial, Phase IV, Publication date from 2008/01/01 to 2015/12/31, Humans, English.			EMBASE Filters	([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [article]/lim AND [english]/lim AND [humans]/lim AND [embase]/lim AND [2008-2015]/py		

Database	Search string (including MeSH search terms)	#hits	Date	Database	Search string (including EMTREE search terms)	#hits	Date
Country specific							
PubMed/USA	("United States"[Mesh]) OR ("USA"[AD]) OR ("U.S.A."[Title/Abstract]) OR ("U.S."[Title/Abstract])	479	3-7-2015	EMBASE/USA	united states'/exp OR 'usa':ac OR 'united states':ac OR 'u.s.a.':ab,ti OR 'u.s.':ab,ti	580	28-8-2015
PubMed /JAP	"((""Japan""[Mesh]) OR (""Japan""[AD]) OR (""Japan""[Title/Abstract]) OR (""JPN""[Title/Abstract]) OR (""JP""[Title/Abstract])) Additional filter: Japanese"	135	3-7-2015	EMBASE /JAP	"japan'/exp OR 'japan':ac OR 'japan':ab,ti OR 'jp':ab,ti OR 'jpn':ab,ti Additional filter: [japanese]/lim"	54	28-8-2015
PubMed /KOR	"((""Republic of Korea""[Mesh]) OR (""Republic of Korea""[AD]) OR (""South Korea""[AD]) OR (""Republic of Korea""[Title/Abstract]) OR (""South Korea""[Title/Abstract]) OR (""KOR""[Title/Abstract]) OR (""KR""[Title/Abstract])) Additional filter: Korean"	39	3-7-2015	EMBASE /KOR	"south korea'/exp OR 'republic of korea':ac,ab,ti AND 'south korea':ac,ab,ti OR 'kor':ab,ti OR 'kr':ab,ti Additional filter: [korean]/lim Deleted filters: ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) "	25	28-8-2015
PubMed /CAN	(("Canada"[Mesh]) OR ("Canada"[AD]) OR ("Canada"[Title/Abstract]))	38	3-7-2015	EMBASE /CAN	canada'/exp OR 'canada':ac OR 'canada':ab,ti	92	28-8-2015

Table A3.2 Clinical Trials Search (Clinicaltrials.gov)

Clinicaltrials.gov		Date
Search terms	'ATMP' or 'Advanced therapies' or 'Advanced therapy medicinal product' or 'Regenerative medicine' or 'Cell therapy' or 'Cell-based product' or 'Cell-based therapies' or 'Gene therapy' or 'Tissue engineering' or 'Tissue engineered products'	31-8-2015
Country (#hits)	USA (411); Canada (39); Japan (15); Korea (34)	
First received	From 01/01/2008 to 31/08/2015	

Table A3.3 Clinical Trials Search (country specific)

Database	Search string	#hits	Date	Database	Search string	#hits	Date
ISRCTN/US	ATMP OR Advanced therapies OR Advanced therapy medicinal product OR Regenerative medicine OR Cell therapy OR Cell-based product OR Cell-based therapies OR Gene therapy OR Tissue engineering OR Tissue engineered products	70	31/08/2015	PHRMA	ATMP OR Advanced therapies OR Advanced therapy medicinal product OR Regenerative medicine OR Cell therapy OR Cell-based product OR Cell-based therapies OR Gene therapy OR Tissue engineering OR Tissue engineered products	119	31/08/2015
ISRCTN/CA	ATMP OR Advanced therapies OR Advanced therapy medicinal product OR Regenerative medicine OR Cell therapy OR Cell-based product OR Cell-based therapies OR Gene therapy OR Tissue engineering OR Tissue engineered products OR Tissue	85	31/08/2015	cancerview.ca/CA	ATMP OR Advanced therapies OR Advanced therapy medicinal product OR Regenerative medicine OR Cell therapy OR Cell-based product OR Cell-based therapies OR Gene therapy OR Tissue engineering OR Tissue engineered products	978	31/08/2015
ISRCTN/JP	ATMP OR Advanced therapies OR Advanced therapy medicinal product OR Regenerative medicine OR Cell therapy OR Cell-based product OR Cell-based therapies	8	31/08/2015	NIPH/JP	ATMP OR Advanced therapies OR Advanced therapy medicinal product OR Regenerative medicine OR Cell therapy OR Cell-based product OR Cell-	147	31/08/2015

Database	Search string	#hits	Date	Database	Search string	#hits	Date
	OR Gene therapy OR Tissue engineering OR Tissue engineered products				based therapies OR Gene therapy OR Tissue engineering OR Tissue engineered products		
ISRCTN/SK	ATMP OR Advanced therapies OR Advanced therapy medicinal product OR Regenerative medicine OR Cell therapy OR Cell-based product OR Cell-based therapies OR Gene therapy OR Tissue engineering OR Tissue engineered products	14	31/08/2015	CRIS/SK	ATMP OR Advanced therapies OR Advanced therapy medicinal product OR Regenerative medicine OR Cell therapy OR Cell-based product OR Cell-based therapies OR Gene therapy OR Tissue engineering OR Tissue engineered products OR Tissue OR Cell OR Gene	172	31/08/2015

Table A3.4 Flow Charts PubMed, EMBASE, Clinicaltrials.gov, country specific and respondents

US					
Database	**EMBASE**	**PubMed**	**Clinicaltrials.gov**		**Country specific / respondents**
Hits	580	479	411		189
Duplicates	56		0		
Reviewers	**Review JW**	**Review MS**	**Review JW**	**Review MS**	
Title	151	185	66	72	
Abstract	39	83			
Full text	82		77		
Selected	58		67		7
Canada					
Database	**EMBASE**	**PubMed**	**Clinicaltrials.gov**		**Country specific / respondents**
Hits	92	38	39		1063
Duplicates	8		0		

Canada					
Reviewers	**Review JW**	**Review MS**	**Review JW**	**Review MS**	
Title	38	39	18	14	
Abstract	12	19			
Full text	15		17		7
Selected	11		15		13
Japan					
Database	**EMBASE**	**PubMed**	**Clinicaltrials.gov**		**Country specific / respondents**
Hits	54	135	15		155
Duplicates	5		0		7
Reviewers	**Review JW**	**Review MS**	**Review JW**	**Review MS**	
Title	59	73	9	10	
Abstract	26	57			
Full text	55		10		104
Selected	40		7		84
South Korea					
Database	**EMBASE**	**PubMed**	**Clinicaltrials.gov**		**Country specific / respondents**
Hits	25	39	34		186
Duplicates	0		0		
Reviewers	**Review JW**	**Review MS**	**Review JW**	**Review MS**	
Title	28	28	16	22	
Abstract	9	13			
Full text	19		16		24
Selected	8		14		21

Annex 4. Databases and websites covering authorised clinical trials

Table A4.1 Databases and websites covering authorised clinical trials and approved advanced therapies in each jurisdiction

Country	Database	Website / Source	Included in search
US	Clinical Trials - US (U.S. National Institutes of Health)	https://clinicaltrials.gov/ct2/results/map/click?map.x=174&map.y=176	Yes
	Clinical Trials - US	http://www.phrma.org	Yes
Canada	Clinical Trials Database (Health Canada)	http://ctdb-bdec.hc-sc.gc.ca/ctdb-bdec/index-eng.jsp	Yes
	Clinical Trials – Canada (U.S. National Institutes of Health)	https://clinicaltrials.gov/ct2/results/map/click?map.x=150&map.y=92	Yes
Japan	Japan Primary Registries Network (JPRN): 1. University Hospital Medical Information Network (UMIN): 2. Japan Pharmaceutical Information Centre - Clinical Trials Information (JapicCTI) 3. Japan Medical Association - Centre for Clinical Trials (JMACCT):	http://rctportal.niph.go.jp/en/index http://www.umin.ac.jp/ctr/ http://www.clinicaltrials.jp/user/cte_main_e.jsp https://dbcentre3.jmacct.med.or.jp/jmactr/Default_Eng.aspx	Yes
	Clinical Trials – Japan (U.S. National Institutes of Health)	https://clinicaltrials.gov/ct2/search/map/click?map.x=683&map.y=177	Yes
South Korea	Clinical Research Information Service (CRiS)	https://cris.nih.go.kr/cris/en/search/basic_search.jsp	Yes
	Clinical Trials – South Korea (U.S. National Institutes of Health)	https://clinicaltrials.gov/ct2/search/map/click?map.x=642&map.y=215	Yes
Additional databases	ISRCTN registry (World Health Organisation, International Committee of Medical Journal Editors)	http://www.isrctn.com/	Yes
	PubMed (US National Library of Medicine National Institutes of Health)	http://www.ncbi.nlm.nih.gov/pubmed	Yes
	EMBASE (Elsevier)	http://www.elsevier.com/online-tools/embase	Yes

Annex 5. Full search strategy and inclusion criteria for the analysis of the regulatory framework governing advanced therapies

Step 1: Websites of competent authorities

Websites considered are provided in the Table below.

Table A5.1 Websites of competent authorities

Jurisdiction	Competent authorities	Legal and regulatory document websites
USA	Food and Drug Administration (FDA)	http://www.fda.gov (general website) http://www.fda.gov/RegulatoryInformation/Legislation/default.htm http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
Canada	Health Canada	http://www.hc-sc.gc.ca (general website) http://www.hc-sc.gc.ca/dhp-mps/brgtherap/legislation/index-eng.php (legal documents) http://laws-lois.justice.gc.ca/
Japan	Pharmaceuticals and Medical Devices Agency (PMDA); Ministry of Health, Labour and Welfare (MHLW)	http://www.pmda.go.jp/english/rs-sb-std/rs/index.html (general website) http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/index.html http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/index.html (Japanese only)
South Korea	Ministry of Food and Drug Safety (MFDS)	http://www.mfds.go.kr/eng/index.do?searchKeyCode=123&nMenuCode=44 (general website) http://www.gsrac.org/eng_about/ http://www.mfds.go.kr/index.do?mid=685 (Korean only)

Step 2 and 3: Structured and free search

Databases

Pubmed (single query)
Scopus (single query)
Web of Sciences (single query)
Google Scholar (multiple queries)

Key search terms

In all searches the following key terms were used to search in the title, abstract and keywords (i.e. MeSH terms, emtree terms) of all indexed publications:

Terms describing advanced therapies:

- ATMP;
- Advanced therapy;

- Advanced therapies;
- Regenerative medicine;
- Cell therapy;
- Cell therapies;
- Cell-based therapy;
- Cell-based therapies;
- Human cellular therapy;
- Stem cells;
- Gene therapy;
- Gene therapies
- Tissue engineering;
- Tissue engineered;
- HCT/Ps.

Terms describing regulatory framework:

- Regulation;
- Legislation;
- Law;
- Policy;
- Act;
- Guideline;
- Approval;
- Authorisation;
- Marketing;
- Post-marketing;
- Quality;
- Manufacturing;
- GMP;
- GLP;
- GCP;
- Compassionate use;
- Special access;
- Expanded access;
- New drug submission;
- New drug application;
- Investigational new drug;
- Clinical trial notification.

Terms describing United States:[11]

- FDA;
- Food and Drug Administration;
- *Office of cellular, tissue and gene therapies;*
- OCTGT.

Terms describing Canada:

- Canada (also captures all cases of "Health Canada": the regulatory agency in Canada).

Terms describing Japan:

- Japan;
- PMDA;
- Pharmaceuticals and Medical Devices Agency;
- *Office of Cellular and Tissue based products;*
- Ministry of Health, labour and welfare;
- MHLW.

Terms describing South Korea:

- Korea;
- Ministry of Food and Drug Safety;
- MFDS;
- National Institute of Food and Drug Safety Evaluation;
- NIFDS.

Publication types

No restrictions on publication type.

Publication fields

Title, abstract, keyword were searched in Pubmed, Scopus and Web of Science. Full-text was searched in Google Scholar.

Query:

Queries were structured by entering different terms describing individual elements (i.e. advanced therapies, regulatory framework and jurisdictions) using "OR" operators and combining terms of elements using "AND" operators.

An example is provided below:

("term describing jurisdiction" OR "term describing jurisdiction")

AND

[11] We did not include the term 'United States' given that this rendered an excessive number of publications, while it is also highly likely that most publications describing the regulatory framework in the US will refer to the Food and Drug Administration (FDA).

("term describing advanced therapies" OR "term describing advanced therapies")

AND

("term describing regulatory framework" OR "term describing regulatory framework")

Period

January 1, 2008 to July 2015

Results

Flowcharts of the retrieved and included documents are provided below for each jurisdiction.

Figure A5.1 Flowchart and results US

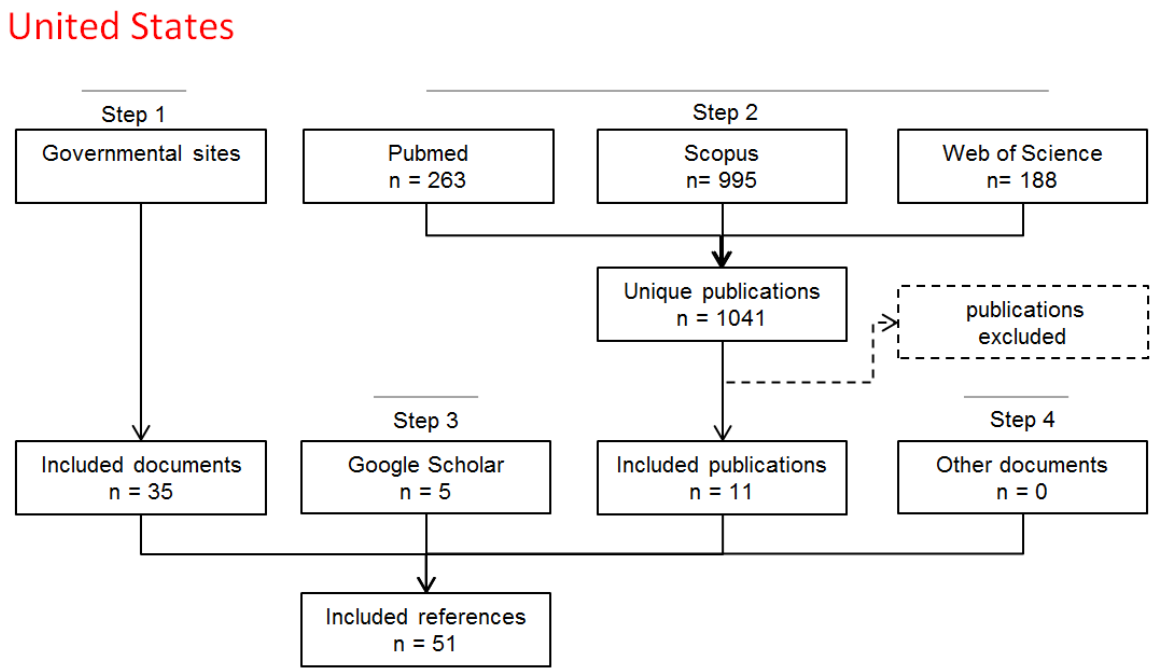


Figure A5.2 Flowchart and results Canada

Canada

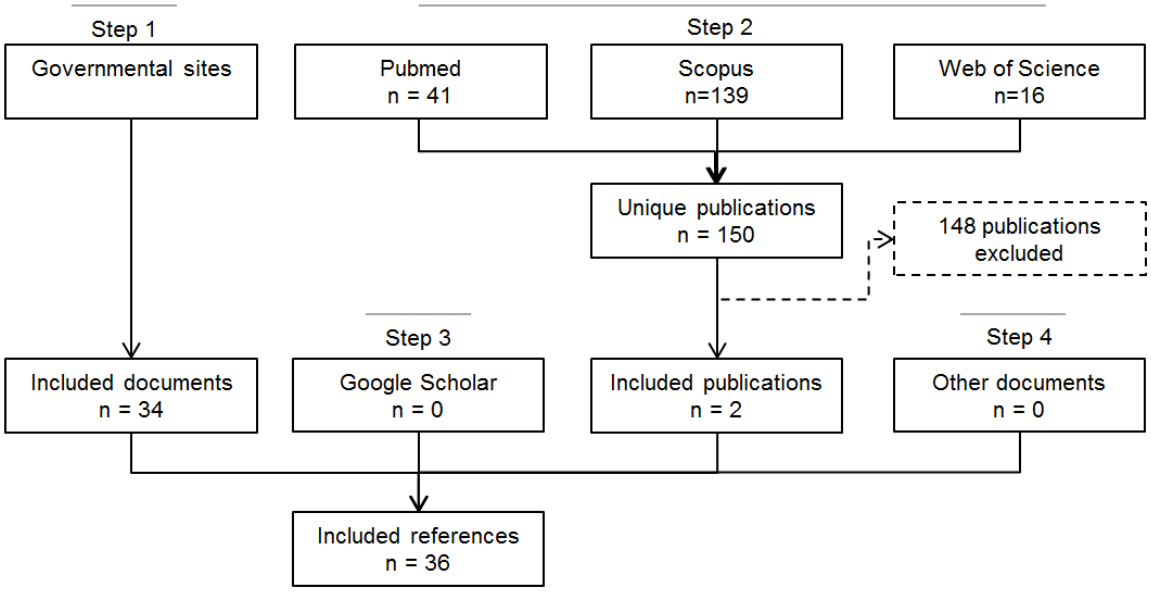


Figure A5.3 Flowchart and results Japan

Japan

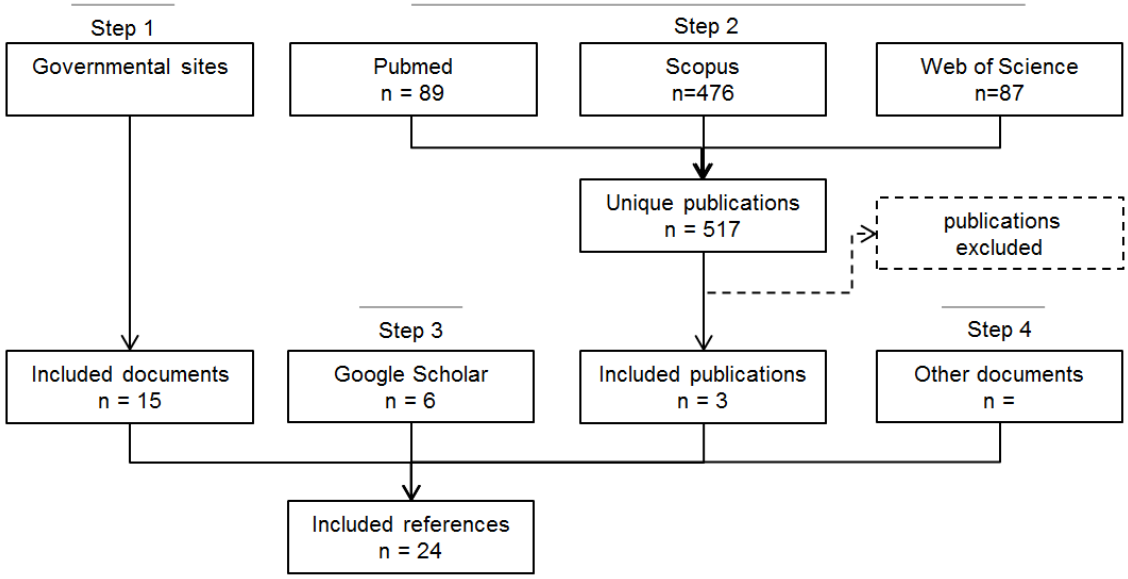
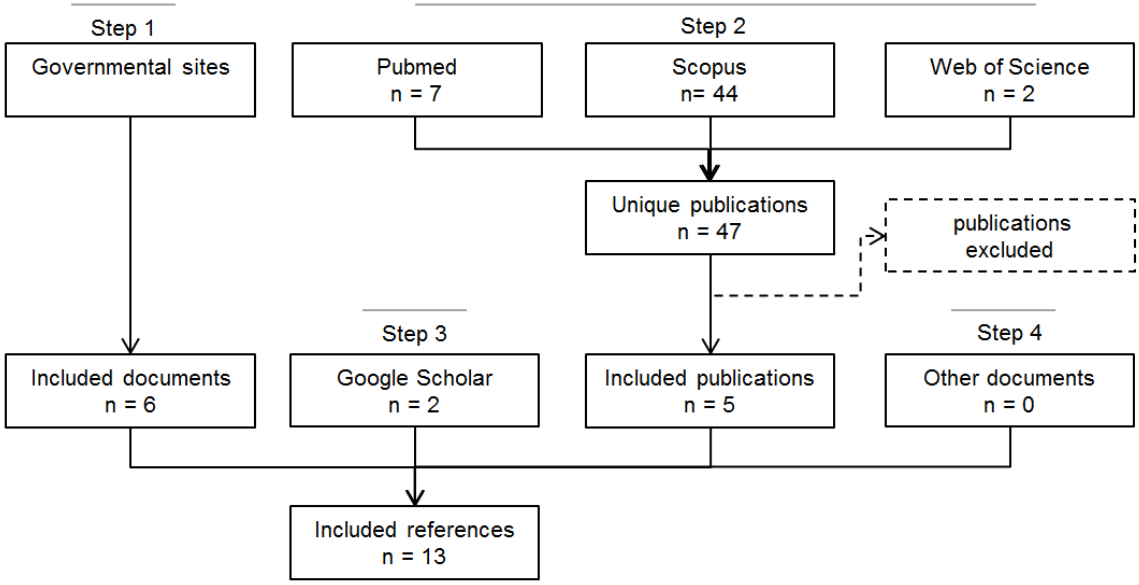


Figure A5.4 Flowchart and results South Korea

South Korea



Annex 6. Advanced therapies authorised for commercialisation

Table A6.1 Advanced therapies authorised for commercialisation (part A)

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
Rank	*Cell, tissue or gene therapy*	*Description of product*	*Marketing*	*Registered name*	*Under approval or under other schemes (i.e. clinical trial, compassionate use programmes, medical practice*	*If applicable*	*If applicable*	*Features that governs the commercialisation procedure (i.e. reduced data requirements, faster approval procedure etc.)*	*High level categorisation: e.g. infectious, cancer, blood, metabolic, nervous system, ocular, ear, cardiovascular, respiratory, digestive, skin/tissue, musculoskeletal*	*Autologous or Allogeneic*
US										
1	Autologous Fibroblasts	Indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.	Azficel-T	Laviv	Approval	22 December 2010	2011	N/R	12 Diseases of the skin and subcutaneous tissue	Autologous
2	Autologous Cultured Chondrocytes	Indicated for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical	Carticel	Autologous Cultured Chondrocytes	Approval	N/R	1997	N/R	13 Diseases of the musculoskeletal system and connective tissue	Autologous

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft).								
3	Biologic response modifier	For intravesical use in the treatment and prophylaxis of carcinoma in situ (CIS) of the urinary bladder and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumours following transurethral resection (TUR).	TheraCys	(Bacillus Calmette-Guerin) BCG Live (Intravesical)	Approval	N/R	2012	N/R	2 Neoplasms	Autologous
4	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	Is an allogeneic cellularized scaffold product indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults.	Gintuit	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	Approval	N/R	2012	N/R	11 Diseases of the digestive system	Allogeneic
5	Autologous Cellular Immuno-therapy	For the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.	Provenge	Sipuleucel-T	Approval	N/R	2010	N/R	2 Neoplasms	Autologous
Canada										
1	Allogeneic Bone Marrow	Prochymal is indicated in the management of acute Graft versus Host Disease (aGvHD) in	Prochymal	Remestemcel-L, Adult Human	Conditional Approval	July 2010 (Newsarticle published by	2012	N/R	19 Injury, poisoning and certain other	Allogeneic

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		paediatric patients. Acute GvHD should be refractory to treatment with systemic corticosteroid therapy and/or other immunosuppressive agents. Prochymal may be used for Grades C and D of the disease in any organ. Prochymal may also be used in the management of Grade B aGvHD involving any visceral organ, including the gastrointestinal (GI) tract and the liver, but excluding skin. Prochymal is the first stem cell therapy indicated for clinical use in patients, specifically for children. It is also the first in a new class of therapeutic agents.		Mesenchymal Stem Cells (hMSCs)		Osiris Therapeutics)			consequences of external causes	
Japan										
1	Autologous Cultured Epidermis	"The product, a patient's own skin tissue is collected, cultured and isolated epidermal cells are used for the patient himself by forming into a sheet ""autologous cultured epidermis"". This product is transplanted into the reconstructed dermis, to close the wound by epithelialization to	JACE	Autologous Cultured Epidermis	Approval	6 October 2004	2007	Fast track	12 Diseases of the skin and subcutaneous tissue	Autologous

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		engraftment."								
2	Autologous Cultured Cartilage	An orthopedic surgeon carries out minimally invasive arthroscopic surgery (keyhole surgery) to collect a small amount of cartilage from the knee. This cartilage is sent to J-TEC and cultured after having been mixed with atelocollagen gel and shaped into a three-dimensional form. During the culture period, which lasts about four weeks, the cartilage cells (chondrocytes) proliferate and eventually reach a state closely resembling the properties of the original cartilage. This method is known as three-dimensional culture, and it is outstanding for the fact that it enables chondrocytes to be cultured while retaining their original properties.	JACC	Autologous Cultured Cartilage	Approval	24 August 2009	2012	N/R	13 Diseases of the musculoskeletal system and connective tissue	Autologous
3	Allogenic mesenchymal stem cells	allogenic mesenchymal stem cell for acute Graft Versus Host Disease (GVHD), a severe complication arising from hematopoietic cell transplants, - See more at:	TEMCELL	Allogenic mesenchymal stem cells	Approval	26-9-2014	2015	Orphan Drug Designation	19 Injury, poisoning and certain other consequences of external causes	Allogeneic

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		http://globenewswire.com/news-release/2015/09/04/766101/10148317/en/Mesoblast-Partner-JCR-Pharmaceuticals-Receives-Recommendation-For-Approval-Of-Mesenchymal-Stem-Cell-Product-In-Japan.html#sthash.ZSdQWvYJ.dpuf								
4	Skeletal myoblast sheets	Autologous skeletal myoblast sheets are cultured from a patient own muscle of thigh and transplanted to patient's heart under the open chest surgery. This transplantation is expected to improve the patient's heart condition significantly. A strong point of the therapy is the absence of any adverse reaction to the cells, since they are harvested from the patient's own body.	HeartSheet	Autologous Skeletal Myoblast Sheets	Conditional approval	30 October 2014	2015	N/R	9 Diseases of the circulatory system	Autologous
South Korea										
1	Allogeneic Umbilical Cord Blood	CARTISTEM® is a drug based on allogeneic umbilical cord blood derived from mesenchymal stem cells. It aims at treating Degenerative Osteoarthritis (knee	Cartistem	Human umbilical cord blood-derived mesenchymal stem cells	Approval	N/R	2012	N/R	13 Diseases of the musculoskeletal system and connective	Allogeneic

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		cartilage defects) caused by degeneration or repeated trauma. CARTISTEM® is applied to lesions through either a surgical method or an arthroscope.							tissue	
2	Autologous Bone Marrow	Hearticellgram®-AMI are bone marrow-derived mesenchymal stem cells (MSCs) used to treat acute myocardial infarction through intracorononary injection.	Hearti-Cellgram	Bone marrow-derived mesenchymal stem cells	Approval	N/R	2011	N/R	9 Diseases of the circulatory system	Autologous
3	Autologous Fat Cell	Cupistem injection is an adipose stem cell therapy product approved for the first time in the world using autologous adipose-derived mesenchymal stem cells manufactured through isolation and culture from patient's adipose tissues. It is used in the treatment of Crohn's Anal Fistula	Cupistem	Autologous adipose-derived mesenchymal stem cells	Approval	N/R	2012	N/R	11 Diseases of the digestive system	Autologous
4	Autologous dermal fibroblast cell cutaneous loss treatment	Cell therapy for burns	LSK autograft	Autologous Keratinocyte	Approval	N/R	2010	N/R	19 Injury, poisoning and certain other consequences of external causes	Autologous

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
5	Autologous Bone Marrow	Neuronata-R is an autologous bone marrow-derived mesenchymal stromal cell, used for the treatment of Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's syndrome.	Neuronata-R	Autologous bone marrow-derived mesenchymal stromal cells (MSCs)	Approval	N/R	2014	N/R	6 Diseases of the nervous system	Autologous
6	Autologous fibroblasts	Skin reproductive cell therapy product. Fibroblast (auto); pimple scar	Cureskin	Skin reproductive cell therapy products	Approval	1 May 2010	2010	N/R	19 Injury, poisoning and certain other consequences of external causes	Autologous
7	Autologous mesenchymal stem cell	Queencell is Stromal Vascular Fraction (SVF) containing autologous mesenchymal stem cells by minimal manipulation of patient's adipose tissues. Indication: regeneration of subcutaneous adipose tissue	Queencell	Autologous adipose-stem cells -with minimal manipulation	Approval	2003	2010	N/R	19 Injury, poisoning and certain other consequences of external causes	Autologous
8	Autologous dermal fibroblast cell cutaneous loss treatment	Cell therapy for subcutaneous fat loss area	Autostem	Adipos-stem cells with minimal manipulation	Approval	N/R	2010	N/R	19 Injury, poisoning and certain other consequences of external causes	Autologous
9	Autologous Bone Marrow	Ossron™ is cultured autologous bone cells for local bone formation. Bone marrow derived	RMS Ossron	Autologous Bone Marrow-derived Stem	Approval	N/R	2009	N/R	19 Injury, poisoning and certain other	Autologous

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		stem cells have shown an ideal osteogenic potential. The stem cell with potent osteogenic property are cultured, multiplied and differentiated into abundant cell number to enhance the bone reconstruction. Ossron™ is performed by three stages: harvesting bone marrow from a patient's own bone, cell culturing at SCP (stem cell platform), and implanting the cultured cells into the defect sites. •Cultured autologous stem cell •Direct and strong bone formation •Long lasting osteogenic factor release •Percutaneous implantation is available		Cell Therapy					consequences of external causes	
10	Cell therapy	Therapy for diabetic foot ulcers	Hyalgraft-3D	Autologous dermal fibroblast cell	Approval	N/R	2007	N/R	1 Certain infectious and parasitic diseases	Autologous
11	Anticancer and immune cell therapy	Biocell Natural Killer Mixture in Patients With DLBCL (Diffuse Large B Cell Lymphoma)	NKM	Autologous Activated lymphocyte	Approval	N/R	2007	N/R	2 Neoplasms	Autologous
12	Autologous immune cell therapy	Activated lymphocyte; liver cancer. Immune cell therapy product made of blood of the	Immuncell-LC	Anticancer and autologous activated	Approval	N/R	2007	N/R	2 Neoplasms	Autologous

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		patient. Adjuvant therapy for patients whose tumour has been removed after curative resection for Hepatocellular Carcinoma (Operation, Radio Frequency Ablation, Percutaneous Ethanol Injection Therapy)		lymphocyte therapy (liver cancer)						
13	Fat stem cell therapy	Autologous cultured adipocytes (ANTG-adip) is produced by well-established techniques including cell harvesting from lipoaspirates, expansion of adipose tissue derived stem cells, and differentiation into pure and immature adipocytes	Adipocel	Autologous cultured adipocytes	Approval	N/R	2007	N/R	19 Injury, poisoning and certain other consequences of external causes	Autologous
14	Autologous dendritic cells	Immunocyte therapeutic agent for renal cell carcinoma: dendritic cells. CreaVax is produced from patient's peripheral blood mononuclear cells(PBMC) by differentiating into dendritic cells after sensitizing with disease specific antigens. Once these autologous dendritic cells are injected to cancer patients, they move to the regional lymph nodes to modulate immune response such as induction of	CreaVax-RCC	Dendritic cell therapy	Approval	N/R	2007	N/R	2 Neoplasms	Autologous

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		cancer-specific cytotoxic T lymphocytes(CTL) to kill tumour cells or immune tolerance against autoimmune antigen.								
15	Autologous keratinocyte cells	Keratheal is an autologous keratinocytes product that was approved bij MFDS in 2006. Keraheal contains high proportion of skin stem cells, which is sprayed onto injured skin in order to promote re-epithelialization and reduce scar formation.	Keraheal	Burn cell therapy	Approval	N/R	2006	N/R	19 Injury, poisoning and certain other consequences of external causes	Autologous
16	Allogeneic keratino-cytes	Kaloderm is made from keratinocytes of one human donor and is among the very few allogeneic cell therapy products now marketed in the world. The cells in Kaloderm, from a certain individual human contain all the good "fertilizer" just as in the healthy human skin. The "fertilizer" is composed of growth factors, cytokines, extra-cellular matrices and collagenases, which work together to stimulate the stem cells in and around the wound and promote healing and decrease scar formation. The	Kaloderm	Allogeneic skin cell therapy	Approval	N/R	2005	N/R	19 Injury, poisoning and certain other consequences of external causes	Allogeneic

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		protein composition, same as human skin cells, guarantees a most effective and safe wound healing.								
17	Autologous keratinocyte and stem cells	Holoderm is a sheet of the patient's own epidermal cells (keratinocytes) which are grown in the lab for roughly 17 days from a tiny piece of his own skin. These sheets are transplanted on the wound just like the patient's own skin. Being autologous and stem cell rich they adhere well and live on, regenerating even the dermal layer over time. Applied for burn wounds.	Holoderm	Autologous skin cell therapy	Approval	N/R	2002	N/R	19 Injury, poisoning and certain other consequences of external causes	Autologous
18	Autologous Chondro-cytes	"Chondron™ is cultured autologous chondrocytes for local cartilage formation in the joint. Management of cartilage defects of the joint has been difficult because articular cartilage has a poor healing capacity as a result of its lack of vessels, nerve supply and its isolation of systemic regulation. ACI has been considered as the best option in contemporary procedures for	Chondron	Cultured autologous chondrocytes	Approval	N/R	2001	N/R	13 Diseases of the musculoskeletal system and connective tissue	Autologous

No.	Type of product	Advanced therapy	Brand name	Proper name	Availability	Submission date	Approval date	Features approval procedure	Therapeutic indication (ICD 10)	If cell-based**
		cartilage regeneration because chondrocyte is the only cell present in cartilage itself and conducts the whole cartilage metabolism. Implantation of Chondron is performed by three stages: harvesting small cartilage from a patient's own cartilage of non-weight bearing area, cell culturing at SCP (stem cell platform), and implanting cultured cartilage cells into the defect sites. Indication: Cartilage defects, Osteoarthritis, Trauma								

Sources approved products:

- US – FDA approved products (http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/default.htm);
- Canada – Health Canada approved products (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2012_prochymal_150026-eng.php);
- Japan - MaSTherCell, the missing link between Asian cell therapy companies and the European market (http://www.masthercell.com/Testimonial-Myriem-Majid-104);
- Japan – PMDA, Regulatory Updates on Cellular Therapy Products in Japan (http://www.pmda.go.jp/files/000164670.pdf);
- South Korea - Perspectives of Korean Pharmaceutical Industries from the World Trend, Sung Wan Kim (http://goo.gl/EP0pW1);
- South Korea - ATMP Development Challenges: From Scientific Advice to Market Authorisation, Peter McArdle (http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/11/WC500196332.pdf);
- South Korea - Cell Therapy Blog: Business news and analysis for executives in the cell therapy and regenerative medicine industry (http://celltherapyblog.blogspot.nl/2011_09_01_archive.html);
- South Korea - Alliance Regenerative Medicine, Clinical Trials & Regenerative Medicine / Advanced Therapies Products (http://alliancerm.org/page/clinical-trials-products);
- South Korea - Stem Cell Assays, Stem cell therapy industry is booming in Korea (http://stemcellassays.com/2012/07/stem-cell-industry-korea/).

Table A6.2 Advanced therapies authorised for commercialisation (part B)

No.	Brand name	Medical device included?	Reimbursement status	Developer	Type of organisation	Man-power (0-50 employees - small; 50-250 employees - medium; >250 employees - big)	Annual turnover	Source
Rank	*Marketing*	*Description of medical device and status of approval*	*Not applied / processing / accepted / denied*	*Name institute/or-ganisation*	*Profit, non-for-profit, academia, SME*	*Number of employees*	*US$*	*Source*
US								
1	Azficel-T	No	Processing	Fibrocell Technologies Inc.	Profit	Small	Total revenue in 2014 of $180.000. Net income 2014 was $25.650.000	http://finance.yahoo.com/q/is?s=FCSC+Income+Statement&annual
2	Carticel	No	Reimbursed	Genzyme Biosurgery (part of Sanofi)	Profit	Big	Total revenue of $4.048.708.000 (2010)	http://www.businesswire.com/news/home/20110216005576/en/Genzyme-Reports-Financial-Results-Fourth-Quarter-2010#.Vfl3SP7ouUk
3	TheraCys	No	Reimbursed	Sanofi Pasteur Limited	Profit	Big	Total revenue in 2014 is $4.460.020	http://www.sanofipasteur.ca/node/14702
4	Gintuit	No	Processing	Organogenesis Incorporated	Profit	Big	Total revenue in 2011 is > $100.000.000	http://www.organogenesis.com/company/company-profile.html
5	Provenge	No	Reimbursed	Dendreon Corporation	Profit	Big	Net product revenue in 2014 was $303.800.000	http://finance.yahoo.com/news/dendreon-announces-strong-commercial-start-133000809.html

No.	Brand name	Medical device included?	Reimbursement status	Developer	Type of organisation	Man-power (0-50 employees - small; 50-250 employees - medium; >250 employees - big)	Annual turnover	Source
Canada								
1	PROCHYMAL	No	Not reimbursed	Osiris Therapeutics Inc. (but acquired by Mesoblast Ltd.)	Public company	Big (51-200)	Total revenue 2014 is $59.867.000	http://finance.yahoo.com/q/is?s=OSIR+Income+Statement&annual
Japan								
1	JACE	No	Reimbursed	Japan Tissue Engineering Co.	Profit	Medium	Revenue 2015 1.321.500.000 yen = $11.004.848.879	http://www.jpte.co.jp/english/ir/financial.html Capitalization: 11,517.425 million yen (as of March 31, 2015)
2	JACC	No	Reimbursed	Japan Tissue Engineering Co., Ltd. (J-TEC)	Profit	Medium	Revenue 2015 1.321.500.000 yen = $11.004.848.879	http://www.jpte.co.jp/english/ir/financial.html Capitalization: 11,517.425 million yen (as of March 31, 2015)
3	TEMCELL	No	Reimbursed	JCR Pharma. Co. (licensed by Mesoblast-former Osiris)	Profit	Big	N/R	N/R
4	HeartSheet	No	In process	Terumo Corporation	Profit	Big	Revenue 2014 489.500.000.000 yen =	http://www.terumo.com/about/profile.html

No.	Brand name	Medical device included?	Reimbursement status	Developer	Type of organisation	Man-power (0-50 employees - small; 50-250 employees - medium; >250 employees - big)	Annual turnover	Source
							$4.074.784.102	
South Korea								
1	Cartistem	No	Not reimbursed	Medipost Co.	Profit	Medium	Revenue 2015 $32.320.000	http://www.gurufocus.com/term/ev2rev/MEPTF/EV%252FRevenue/Medipost%2BCo%2BLtd
2	HeartiCellgram	No	Not reimbursed	FCB PharmiCell Co., Ltd.	Profit	Medium	Revenue 2015 $6.822.375	http://www.securities.com/php/company-profile/KR/PHARMICELL_COLTD_en_1651770.html
3	Cupistem	No	Reimbursed	Anterogen Co., Ltd.	Profit	Small	N/R	http://anterogen.com/main/en/sub03_01.html?type=1
4	LSK autograft	No	N/R	Chabio&tech	Profit	Big	N/R	N/R
5	Neuronata-R	No	Not reimbursed	Corestem Inc.	Profit	Small	Revenue 2015 $12.871.417 (based on revenue/employee rate	http://www.reuters.com/finance/stocks/financialHighlights?symbol=166480.KQ
6	Cureskin	No	Not reimbursed	S. Biomedics	Profit	N/R	N/R	http://www.sbiomedics.com/
7	Queencell	No	Reimbursed	Anterogen Co., Ltd.	Profit	Small	N/R	N/R
8	Autostem	No	N/R	Chabio&tech	Profit	Big	N/R	N/R
9	RMS Ossron	No	Not reimbursed	Sewon Cellontech Co., Ltd.	Profit	Big	Revenue 2014 $202.012.100	http://www.bloomberg.com/research/stocks/financials/financials.asp?ticker=091090:KS

No.	Brand name	Medical device included?	Reimbursement status	Developer	Type of organisation	Man-power (0-50 employees - small; 50-250 employees - medium; >250 employees - big)	Annual turnover	Source
10	Hyalgraft-3D	No	N/R	Chabio&tech	Profit	Big	N/R	N/R
11	NKM	No	N/R	NKBio	Profit	N/R	N/R	N/R
12	Immuncell-LC	No	Not reimbursed	Green Cross Cell	Profit	Medium	Revenue 2015 $5.425.673	http://www.corporateinformation.com/Company-Snapshot.aspx?cusip=C410PY900
13	Adipocel	No	N/R	Antrogen	Profit	Small	N/R	N/R
14	CreaVax-RCC	No	Not reimbursed	JW CreaGene	Profit	Big	Revenue 2014 $4.128.000	http://www.cwp.co.kr/pharma/en/investment/summary.jsp
15	Keraheal	No	Not reimbursed	MCTT	Profit	N/R	N/R	http://www.mctt.co.kr/eng/about/history.jsp
16	Kaloderm	No	Reimbursed	Tego Science	Profit	Small	Revenue 2014 $5.928.540	http://financials.morningstar.com/ratios/r.html?t=191420
17	Holoderm	No	Not reimbursed	Tego Science	Profit	Small	Revenue 2014 $5.928.540	http://financials.morningstar.com/ratios/r.html?t=191420
18	Chondron	No	Reimbursed	Sewon Cellontech	Profit	Big	Revenue 2014 $202.012.100	http://www.bloomberg.com/research/stocks/financials/financials.asp?ticker=091090:KS

Annex 7. Clinical trials of advanced therapies in each jurisdiction

Table A7.1. Clinical trials of advanced therapies in US

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
	Database	*Description of the researched product*	*Research year*	*Tested in humans or not*	*Preclinical-Phase III*	*High level categorisation (ICD-10)*	*Autologous or allogeneic*	*Organisation developing product*	*Profit, non-for-profit, academia*	*Small 0-50 employees, medium 50-250, big >250)*	*Number of employees*	*US$*
1	PubMed/ EMBASE	Mesenchymal precursor cells as adjunctive therapy in recipients of contemporary left ventricular assist devices	2014	Yes	Phase I/II	9 Diseases of the circulatory system	Allogeneic	Mount Sinai School of Medicine	Academia	Big	5000	$ 1.577.532,00
2	PubMed/ EMBASE	AAV2 gene therapy re-administration in three adults with congenital blindness	No.	Yes	Phase I	7 Diseases of the eye and adnexa	N/A	University of Pennsylvania	Academia	Big	4555	$ 881.000.000,00
3	PubMed/ EMBASE	Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): Initial results of a randomised phase 1 trial	2011	Yes	Phase I	9 Diseases of the circulatory system	Autologous	University of Louisville	Academia	Big	6859	$1.217.915.300,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
4	PubMed/ EMBASE	Phase 1 gene therapy for Duchenne muscular dystrophy using a translational optimized AAV vector	2012	Yes	Phase I	6 Diseases of the nervous system	N/A	Duke University Medical Centre	Academia	Big	10024	$ 3.050.000.000,00
5	PubMed/ EMBASE	Chest wall reconstruction with creation of neoribs using mesenchymal cell bone allograft and porcine small intestinal submucosa	2010	Yes	Phase I	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	Oklahoma State University	Academia	Big	N/R	$ 741.872.000,00
6	PubMed/ EMBASE	Off-label use of recombinant human bone morphogenetic protein-2 (rhBMP-2) for reconstruction of mandibular bone defects in humans	2008	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	N/A	University of Washington	Academia	Big	26538	$ 3.914.000.000,00
7	PubMed/ EMBASE	Revascularized tissue transplant and internal transport disk distraction osteogenesis for the reconstruction of complex composite mandibular defects	2011	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	University of Michigan	Academia	Big	44000	$ 5.534.882.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
8	PubMed/ EMBASE	NeoCart, an autologous cartilage tissue implant, compared with micro fracture for treatment of distal femoral cartilage lesions: an FDA phase-II prospective, randomized clinical trial after two years	2012	Yes	Phase III	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Oregon Health and Science Centre	Academia	Big	15098	$ 2.400.000.000,00
9	PubMed/ EMBASE	RNA-based gene therapy for HIV with lentiviral vector-modified CD34 + cells in patients undergoing transplantation for AIDS-related lymphoma	2010	Yes	Phase II	2 Neoplasms	N/A	National Institutes of Health (NIH)	Non-for-profit	N/R		
10	PubMed/ EMBASE	Results from a phase I safety trial of hAADC gene therapy for Parkinson disease	2008	Yes	Phase I/II	6 Diseases of the nervous system	N/A	Lawrence Berkeley National Laboratory	Non-for-profit	Big	3232	$785.000.000,00
11	PubMed/ EMBASE	Gene therapy for pain: results of a phase I clinical trial	2011	Yes	Phase I	18 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	N/A	University of Michigan	Academia	Big	44000	$ 5.534.882.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
12	PubMed/ EMBASE	Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients With Advanced Heart Failure. The CUPID 2 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b)	2014	Yes	Phase II	9 Diseases of the circulatory system	N/A	University of California at San Diego	Academia	Big	29986	$ 3.773.554.000,00
13	PubMed/ EMBASE	Design of a phase 1/2 trial of intracoronary administration of AAV1/SERCA2a in patients with heart failure	2008	Yes	Phase I	9 Diseases of the circulatory system	N/A	Mount Sinai School of Medicine	Academia	Big	5000	$ 1.577.532,00
14	PubMed/ EMBASE	Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: The POSEIDON randomized trial	2012	Yes	Phase I/II	9 Diseases of the circulatory system	Allogeneic	University of Miami Miller School of Medicine	Academia	Big	14604	$ 2.706.500.000,00
15	PubMed/ EMBASE	Adoptive cell therapy for patients with melanoma, using tumour-infiltrating lymphocytes genetically engineered to secrete interleukin-2	2008	Yes	Phase I/II	2 Neoplasms	Autologous	National Cancer Institute (NCI)	Non-for-profit	Big	4000	$ 4.950.000.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
16	PubMed/ EMBASE	Intrathecal gene therapy for treatment of leptomeningeal carcinomatosis	2011	Yes	Phase I	2 Neoplasms	N/A	National Institutes of Health (NIH)	Non-for-profit	N/R		
17	PubMed/ EMBASE	Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: The TAC-HFT randomized trial	2014	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	University of Miami Miller School of Medicine	Academia	Big	14604	$ 2.706.500.000,00
18	PubMed/ EMBASE	A double-blind placebo-controlled clinical evaluation of MultiStem for the treatment of ischemic stroke	2014	Yes	Phase II	6 Diseases of the nervous system	Allogeneic	Georgia Health Sciences University	Academia	Big	N/R	$ 4.371.154.700,00
19	PubMed/ EMBASE	Placental mesenchymal and cord blood stem cell therapy for dilated cardiomyopathy	2008	Yes	Phase I	9 Diseases of the circulatory system	Allogeneic	Medistem Laboratories Inc.	Profit	Small	9	N/R
20	PubMed/ EMBASE	Gene therapy for leber congenital amaurosis caused by RPE65 mutations: Safety and efficacy in 15 children and adults followed up to 3 years	2012	Yes	Phase I	7 Diseases of the eye and adnexa	N/A	University of Pennsylvania	Academia	Big	4555	$ 881.000.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
21	PubMed/ EMBASE	Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID Trial), a First-in-Human Phase 1/2 Clinical Trial	2009	Yes	Phase I/II	9 Diseases of the circulatory system	N/A	San Diego Cardiac Centre (in corporation with National Healt Institutes)	Non-for-profit	N/R	N/R	N/R
22	PubMed/ EMBASE	Calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID): A phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+-ATPase in patients with advanced heart failure	2011	Yes	Phase II	9 Diseases of the circulatory system	N/A	University of Pennsylvania	Academia	Big	4555	$ 881.000.000,00
23	PubMed/ EMBASE	Stem cell therapy for craniofacial bone regeneration: A randomized, controlled feasibility trial	2013	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	University of Michigan	Academia	Big	44000	$ 5.534.882.000
24	PubMed/ EMBASE	Allogeneic human mesenchymal stem cell therapy (Remestemcel-L, Prochymal) as a rescue agent for severe refractory acute graft-versus-host disease in pediatric patients	2014	Yes	Phase II/III	19 Injury, poisoning and certain other consequences of external causes	Allogeneic	Duke University Medical Centre	Academia	Big	10024	$ 3.050.000.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
25	PubMed/ EMBASE	First-in-human mutation-targeted siRNA phase Ib trial of an inherited skin disorder	2010	Yes	Phase I	12 Diseases of the skin and subcutaneous tissue	N/A	University of Utah	Academia	Big	30000	$ 3.123.651.000,00
26	PubMed/ EMBASE	AAV2-GAD gene therapy for advanced Parkinson's disease: A double-blind, sham-surgery controlled, randomised trial	2011	Yes	Phase II	6 Diseases of the nervous system	N/A	Wayne State University School of Medicine	Academia	Big	2790	$ 809.000.000,00
27	PubMed/ EMBASE	Intramyocardial, autologous CD34+ cell therapy for refractory angina	2011	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Northwestern University	Academia	Big	3334	$ 2.149.029,00
28	PubMed/ EMBASE	A randomized, controlled pilot study of autologous CD34+ cell therapy for critical limb ischemia	2012	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Northwestern Memorial Hospital and Feinberg Cardiovascular Research Institute	Non-for-profit	Big	25000	$ 3.885.630.000,00
29	PubMed/ EMBASE	Evaluation of the delivery of mesenchymal stem cells into the root canal space of necrotic immature teeth after clinical regenerative endodontic procedure	2011	Yes	Phase I/II	11 Diseases of the digestive system	N/R	University of Texas Health Science Centre at San Antonio	Academia	Big	5076	$ 885.223.383,32

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
30	PubMed/ EMBASE	Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): A prospective, randomised phase 1 trial	2012	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Cedars-Sinai Heart Institute	Non-for-profit	Big	10243	$ 2.746.100.000,00
31	PubMed/ EMBASE	Intracoronary cardiosphere-derived cells after myocardial infarction: Evidence of therapeutic regeneration in the final 1-year results of the CADUCEUS trial (CArdiosphere-derived aUtologous stem CElls to reverse ventricular dysfunction)	2014	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Cedars-Sinai Heart Institute	Non-for-profit	Big	10243	$ 2.746.100.000,00
32	PubMed/ EMBASE	Phase I study of H5.020CMV.PDGF-beta to treat venous leg ulcer disease	2009	Yes	Phase I	9 Diseases of the circulatory system	N/A	University of Pennsylvania School of Medicine	Academia	Big	24293	$ 4.900.000.000,00
33	PubMed/ EMBASE	Clinical application of an acellular biologic scaffold for surgical repair of a large, traumatic quadriceps femoris muscle defect	2010	Yes	Phase I	19 Injury, poisoning and certain other consequences of external causes	Allogeneic	United States Army Institute of Surgical Research	Non-for-profit	N/R	N/R	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
34	PubMed/ EMBASE	Safety and tolerability of human placenta-derived cells (PDA001) in treatment-resistant crohn's disease: a phase 1 study	2013	Yes	Phase I	11 Diseases of the digestive system	Allogeneic	Mount Sinai School of Medicine	Academia	Big	5000	$ 1.577.532,00
35	PubMed/ EMBASE	Effectiveness of haemodialysis access with an autologous tissue-engineered vascular graft: a multicentre cohort study	2009	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	Cytograft Tissue Engineering	Profit	Medium	Medium	N/R
36	PubMed/ EMBASE	Safety, tolerability, and clinical outcomes after intraarticular injection of a recombinant adeno-associated vector containing a tumour necrosis factor antagonist gene: results of a phase 1/2 Study	2009	Yes	Phase I/II	2 Neoplasms	N/A	Swedish Medical Centre	Non-for-profit	Big	9450	$ 2.027.470.000,00
37	PubMed/ EMBASE	Limb-girdle muscular dystrophy type 2D gene therapy restores (alpha)-sarcoglycan and associated proteins	2009	Yes	Phase I	6 Diseases of the nervous system	N/A	Ohio State University	Academia	Big	23000	$ 5.787.000.000,00
38	PubMed/ EMBASE	Acellular dermal matrix and negative pressure wound therapy: a tissue-engineered alternative to free tissue	2012	Yes	Phase I	19 Injury, poisoning and certain other consequences of	N/R	The Methodist Hospital	Non-for-profit	Big	18000	$ 2.616.169.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		transfer in the compromised host				external causes						
39	PubMed/ EMBASE	Sinus augmentation in two patients with severe posterior maxillary height atrophy using tissue-engineered bone derived from autologous bone cells: a case report	2011	Yes	Phase I	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Columbia University College of Dental Medicine	Academia	Big	11136	$ 3.310.000.000,00
40	PubMed/ EMBASE	Cancer regression and neurological toxicity following anti-MAGE-A3 TCR gene therapy	2014	Yes	Phase I/II	2 Neoplasms	N/A	National Cancer Institute (NCI)	Non-for-profit	Big	4000	$ 4.950.000.000,00
41	PubMed/ EMBASE	Autologous bone marrow mononuclear cell therapy is safe and promotes amputation-free survival in patients with critical limb ischemia	2011	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Indiana University School of Medicine	Academia	Big	7130	$ 2.721.541,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
42	PubMed/EMBASE	Rationale and Design of the Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis in Dilated Cardiomyopathy (The POSEIDON-DCM Study): A phase I/II, Randomized Pilot Study of the Comparative Safety and Efficacy of Transendocardial Injection of Autologous Mesenchymal Stem Cell vs. Allogeneic Mesenchymal Stem Cells in Patients with Non-ischemic Dilated Cardiomyopathy	2014	Yes	Phase I/II	9 Diseases of the circulatory system	Allogeneic	University of Miami Miller School of Medicine	Academia	Big	14604	$ 2.706.500.000,00
43	PubMed/ EMBASE	Hereditary inclusion body myopathy: single patient response to GNE gene Lipoplex therapy	2010	Yes	Phase I	6 Diseases of the nervous system	N/A	Mary Crowley Cancer Research Centres	Non-for-profit	Medium	83	$ 9.000.000,00
44	PubMed/ EMBASE	Potential of Advexin: a p53 gene-replacement therapy in Li-Fraumeni syndrome	2008	Yes	Phase I	2 Neoplasms	N/A	Baylor Sammons Cancer Centre	Non-for-profit	N/R	N/R	N/R
45	PubMed/ EMBASE	Tissue-engineered bilayered cell therapy for the treatment of oral mucosal defects: a case series	2010	Yes	Phase I	1 Certain infectious and parasitic diseases	Allogeneic	Harvard School of Dental Medicine	Academia	Big	12426	$ 617.000.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
46	PubMed/ EMBASE	Augmentation vaginoplasty of colonic neovagina stricture using oral mucosa graft	2010	Yes	Phase I	14 Diseases of the genitourinary system	Autologous	University of Michigan Health System	Academia	Big	26000	$ 2.500.000.000,00
47	PubMed/ EMBASE	An open-label dose escalation study to evaluate the safety of administration of nonviral stromal cell-derived factor-1 plasmid to treat symptomatic ischemic heart failure	2013	Yes	Phase I	9 Diseases of the circulatory system	N/A	Northeast Ohio Medical University	Academia	N/R	N/R	$ 70.504.752,00
48	PubMed/ EMBASE	Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: The FOCUS-CCTRN trial	2012	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Texas Heart Institute	Non-for-profit	N/R	N/R	N/R
49	PubMed/ EMBASE	A phase 3, randomized, double-blinded, active-controlled, unblinded standard of care study assessing the efficacy and safety of intramyocardial autologous CD34+ cell administration in patients	2013	Yes	Phase III	9 Diseases of the circulatory system	Autologous	Duke University Medical Centre	Academia	Big	10024	$ 3.050.000.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		with refractory angina: design of the RENEW study										
50	PubMed/ EMBASE	Long-term follow-up assessment of a phase 1 trial of angiogenic gene therapy using direct intramyocardial administration of an adenoviral vector expressing the VEGF121 cDNA for the treatment of diffuse coronary artery disease	2013	Yes	Phase I	9 Diseases of the circulatory system	N/A	Stony Brook University Medical Center	Academia	Big	5981	$1.620.844.000,00
51	PubMed/ EMBASE	Phase i trial of bi-shRNAi furin/GMCSF DNA/autologous tumour cell vaccine (FANG) in advanced cancer	2012	Yes	Phase I	2 Neoplasms	N/A	Mary Crowley Cancer Research Centres	Non-for-profit	Medium	83	$ 9.000.000,00
52	PubMed/ EMBASE	Kidney protection and regeneration following acute injury: progress through stem cell therapy	2012	Yes	Phase I	19 Injury, poisoning and certain other consequences of external causes	Allogeneic	Brigham and Women's Hospital,	Non-for-profit	Big	1200	$ 1.889.577.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
53	PubMed/ EMBASE	Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: The LateTIME randomized trial	2011	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	Minneapolis Heart Institute at Abbott Northwestern Hospital	Non-for-profit	N/R	N/R	N/R
54	PubMed/ EMBASE	Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: The time randomized trial	2012	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Minneapolis Heart Institute at Abbott Northwestern Hospital	Non-for-profit	N/R	N/R	N/R
55	PubMed/ EMBASE	LateTIME: A Phase-II, randomized, double-blinded, placebo-controlled, pilot trial evaluating the safety and effect of administration of bone marrow mononuclear cells 2 to 3 weeks after acute myocardial infarction	2010	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Baylor University School of Medicine	Academia	Big	8924	$ 604.276.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
56	PubMed/ EMBASE	Results of a phase 1, randomized, double-blind, placebo-controlled trial of bone marrow mononuclear stem cell administration in patients following ST-elevation myocardial infarction	2010	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Minneapolis Heart Institute at Abbott Northwestern Hospital	Non-for-profit	N/R	N/R	N/R
57	PubMed/ EMBASE	A placebo-controlled, randomized trial of mesenchymal stem cells in COPD	2013	Yes	Phase I/II	10 Diseases of the respiratory system	Allogeneic	University of Vermont College of Medicine	Academia	Big	2340	$ 545.295.000,00
58	PubMed/ EMBASE	A phase 2 trial of surgery with perioperative INGN 201 (Ad5CMV-p53) gene therapy followed by chemoradiotherapy for advanced, resectable squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx: report of the Southwest Oncology Group	2009	Yes	Phase II	2 Neoplasms	N/A	Wayne State University	Academia	Big	2790	$ 809.000.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
59	Clinicaltrials.gov	Long-term follow-up to the DEVO pivotal trial of Dermagraft® to treat venous leg ulcers	2013	Yes	Phase III	9 Diseases of the circulatory system	Allogeneic	Shire Regenerative Medicine Inc. (product developed by Dermagraft Inc.)	Profit	Big	5300	$4.757.000,00
60	Clinicaltrials.gov	Pivotal trial of Dermagraft® to treat venous leg ulcers	2009	Yes	Phase III	9 Diseases of the circulatory system	Allogeneic	Shire Regenerative Medicine Inc. (product developed by Dermagraft Inc.)	Profit	Big	5300	$4.757.000,00
61	Clinicaltrials.gov	A study of the efficacy and safety of ABH001 in the treatment of patients with epidermolysis bullosa who have wounds that are not healing	2012	Yes	Phase III	17 Congenital malformations, deformations and chromosomal abnormalities	Allogeneic	Shire Regenerative Medicine Inc.	Profit	Big	5300	$4.757.000,00
62	Clinicaltrials.gov	Muscle progenitor cell therapy for urinary incontinence	2013	Yes	Phase I/II	14 Diseases of the genitourinary system	Autologous	Wake Forest School of Medicine	Academia	Big	1650	$ 1.190.393.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
63	Clinicaltrials.gov	Enriched autologous fat grafting for treating pain at amputation sites	2012	Yes	Phase I/II	19 Injury, poisoning and certain other consequences of external causes	Autologous	University of Pittsburgh	Academia	Big	12334	$ 2.007.362.000,00
64	Clinicaltrials.gov	Pivotal trial of Dermagraft® to treat diabetic foot ulcers	2010	Yes	Phase III	1 Certain infectious and parasitic diseases	Allogeneic	Shire Regenerative Medicine Inc. (product developed by Dermagraft Inc.)	Profit	Big	5300	$4.757.000,00
65	Clinicaltrials.gov	Dermagraft® for the treatment of patients with diabetic foot ulcers	2010	Yes	Phase III	1 Certain infectious and parasitic diseases	Allogeneic	Shire Regenerative Medicine Inc. (product developed by Dermagraft Inc.)	Profit	Big	5300	$4.757.000,00
66	Clinicaltrials.gov	Evaluation of safety and exploratory efficacy of Cartistem®, a cell therapy product for articular cartillage defects	2012	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	Medipost Co.	Profit	Medium	200	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
67	Clinicaltrials.gov	Phase II combination stem cell therapy for the treatment of severe leg ischemia	2008	Yes	Phase II	9 Diseases of the circulatory system	Autologous	TCA Cellular Therapy	Profit	N/R	N/R	N/R
68	Clinicaltrials.gov	Stem cell therapy to improve burn wound healing	2014	Yes	Phase I	19 Injury, poisoning and certain other consequences of external causes	Allogeneic	University of Miami	Academia	Big	14604	$ 2.706.500.000,00
69	Clinicaltrials.gov	Cell therapy for cranofacial bone defects	2012	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	University of Michigan	Academia	Big	44000	$ 5.534.882.000
70	Clinicaltrials.gov	Combination of stem cell therapy for the treatment of severe coronary ischemia	2008	Yes	Phase I	9 Diseases of the circulatory system	Autologous	TCA Cellular Therapy	Profit	N/R	N/R	N/R
71	Clinicaltrials.gov	Cell therapy for metastatic melanoma using CD8 enriched tumour infiltrating lymphocytes	2010	Yes	Phase I/II	2 Neoplasms	N/R	National Cancer Institute (NCI)	Non-for-profit	Big	4000	$ 4.950.000.000
72	Clinicaltrials.gov	Mesenchymal stem cell therapy for lung rejection	2014	Yes	Phase I	10 Diseases of the respiratory system	Autologous	Mayo Clinic	Non-for-profit	Big	59500	$ 9.760.600.000,00
73	Clinicaltrials.gov	Phase II combination stem cell therapy for the	2008	Yes	Phase II	9 Diseases of the circulatory	Autologous	TCA Cellular Therapy	Profit	Small	Small	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		treatment of severe coronary ischemia (CI)				system						
74	Clinicaltrials.gov	Mesenchymal stem cell therapy in multiple system atrophy	2014	Yes	Phase I	6 Diseases of the nervous system	Autologous	Mayo Clinic	Non-for-profit	N/R		
75	Clinicaltrials.gov	An investigation of the safety of 4 different doses of autologous muscle derived cells as a therapy for stress urinary incontinence	2009	Yes	Phase II	14 Diseases of the genitourinary system	Autologous	Cook MyoSite	Profit	Medium	Medium	N/R
76	Clinicaltrials.gov	Stem cell injection to treat heart damage during open heart surgery	2012	Yes	Phase I	9 Diseases of the circulatory system	Autologous	National Heart, Lung, and Blood Institute (NHLBI)	Non-for-profit	Big	N/R	$ 3.000.000.000,00
77	Clinicaltrials.gov	Treatment alveolar bone defects using aastrom biosciences autologous tissue repair cell therapy	2008	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	University of Michigan	Academia	Big	44000	$ 5.534.882.000
78	Clinicaltrials.gov	A dose-escalation safety trial for intrathecal autologous mesenchymal stem cell therapy in amyotrophic lateral sclerosis	2012	Yes	Phase I	6 Diseases of the nervous system	Autologous	Mayo Clinic	Non-for-profit	Big	59500	$ 9.760.600.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
79	Clinicaltrials.gov	Autologous cell therapy for stress urinary incontinence in males following prostate surgery	2014	Yes	Phase I/II	14 Diseases of the genitourinary system	Autologous	Cook MyoSite	Profit	Medium	Medium	N/R
80	Clinicaltrials.gov	Prospective randomized study of mesenchymal stem cell therapy in patients undergoing cardiac surgery (PROMETHEUS)	2008	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	National Heart, Lung, and Blood Institute (NHLBI)	Non-for-profit	Big	N/R	$ 3.000.000.000,00
81	Clinicaltrials.gov	An efficacy, safety and tolerability study of Ixmyelocel-T administered via transendocardial catheter-based injections to subjects with heart failure due to ischemic dilated cardiomyopathy (IDCM)	2012	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Vericel Co.	Profit	Medium	187	$50.450.000,00
82	Clinicaltrials.gov	An efficacy and safety study of Ixmyelocel-T in patients with critical limb ischemia (CLI)	2011	Yes	Phase III	9 Diseases of the circulatory system	Autologous	Vericel Co.	Profit	Medium	187	$50.450.000,00
83	Clinicaltrials.gov	Research with retinal cells derived from stem cells for myopic macular degeneration	2014	Yes	Phase I/II	7 Diseases of the eye and adnexa	Allogeneic	University of California (Ocata Therapeutics Inc. as collaborator)	Academia	Big	32110	$ 4.930.000.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
84	Clinicaltrials.gov	Evaluation of Prochymal® for treatment-refractory moderate-to-severe Crohn's disease	2010	Yes	Phase III	11 Diseases of the digestive system	Allogeneic	Mesoblast Ltd.	Profit	Medium	115	$29.580.000,00
85	Clinicaltrials.gov	Autologous muscle derived cells for female urinary sphincter repair	2013	Yes	Phase III	14 Diseases of the genitourinary system	Autologous	Cook MyoSite	Profit	Medium	Medium	N/R
86	Clinicaltrials.gov	Phase 2, randomized, double blind, placebo controlled multicenter study of autologous MSC-NTF cells in patients with ALS	2013	Yes	Phase II	6 Diseases of the nervous system	Autologous	Brainstrom-Cell Therapeutics	Profit	Small	19	N/R
87	Clinicaltrials.gov	Adipose derived regenerative cellular therapy of chronic wounds	2014	Yes	Phase II	12 Diseases of the skin and subcutaneous tissue	Autologous	Tower Outpatient Surgical Centre	Non-for-profit	N/R	N/R	N/R
88	Clinicaltrials.gov	A safety study of CNTO 2476 in patients with age-related macular degeneration	2010	Yes	Phase I/II	7 Diseases of the eye and adnexa	Allogeneic	Janssen Research & Development, LLC.	Profit	Big	3855	$ 2.443.557,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
89	Clinicaltrials.gov	Safety and effectiveness of banked cord blood or bone marrow stem cells in children with cerebral palsy (CP)	2013	Yes	Phase II	6 Diseases of the nervous system	Autologous	University of Texas Health Science Centre at San Antonio	Academia	Big	5076	$ 885.223.383,32
90	Clinicaltrials.gov	Bone tissue engineering using autologous bone repair cell (BRC) therapy for sinus floor bone augmentation	2009	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	University of Michigan	Academia	Big	44000	$ 5.534.882.000
91	Clinicaltrials.gov	A phase 2 trial of AMI Multistem® therapy in subjects with non-ST elevation acute myocardial infarction	2014	Yes	Phase II	9 Diseases of the circulatory system	Allogeneic	Athersys Inc. (NHLBI as collaborator)	Profit	Small	57	$1.580.000,00
92	Clinicaltrials.gov	Laboratory-treated T cells in treating patients with high-risk relapsed acute myeloid leukemia, myelodysplastic syndrome, or chronic myelogenous leukemia previously treated with donor stem cell transplant	2011	Yes	Phase I/II	2 Neoplasms	N/R	Fred Hutchinson Cancer Research Centre (NCI as collaborator)	Non-for-profit	Big	2700	$ 436.550.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
93	Clinicaltrials.gov	Adipose -derived regenerative cells in total knee arthroplasty	2014	Yes	N/R	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Fondren Orthopedic Group L.L.P. (InGeneron Inc. as collaborator)	Profit	Medium	Medium	$160.000,00
94	Clinicaltrials.gov	Autologous CD-19-specific T-cell infusion	2009	Yes	Phase I	2 Neoplasms	Autologous	M.D. Anderson Cancer Centre (NCI, Ziopharm & Intrexon Co. as collaborators)	Non-for-profit	Big	20000	$ 4.412.923.943,00
95	Clinicaltrials.gov	T-cell receptor immunotherapy targeting MAGE-A3 for patients with metastatic cancer who are HLA-A*01 positive	2014	Yes	Phase I/II	2 Neoplasms	Autologous	National Cancer Institute (NCI)	Non-for-profit	Big	4000	$ 4.950.000.000
96	Clinicaltrials.gov	T-cell receptor immunotherapy targeting MAGE-A3 for patients with metastatic cancer who are HLA-DP0401 positive	2014	Yes	Phase I/II	2 Neoplasms	Autologous	National Cancer Institute (NCI)	Non-for-profit	Big	4000	$ 4.950.000.000
97	Clinicaltrials.gov	Stem cell study for subjects with congestive heart failure	2008	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Douglas Losordo	Academia	N/R		

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
98	Clinicaltrials.gov	Use of autologous bone marrow aspirate concentrate in painful knee osteoarthritis	2013	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Mayo Clinic	Non-for-profit	Big	59500	$ 9.760.600.000,00
99	Clinicaltrials.gov	Laboratory-treated donor cord blood cell infusion following combination chemotherapy in treating younger patients with relapsed or refractory acute myeloid leukemia	2012	Yes	Phase I/II	2 Neoplasms	Allogeneic	Fred Hutchinson Cancer Research Centre (NCI as collaborator)	Non-for-profit	Big	2700	$ 436.550.000,00
100	Clinicaltrials.gov	Injections of FloGraft therapy, autologous stem cells, or platelet rich plasma for the treatment of degenerative joint pain	2013	Yes	Phase II/III	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Arizona Pain Specialists	Non-for-profit	Medium	51 - 200 employees	N/R
101	Clinicaltrials.gov	Gene therapy for fanconi anemia	2011	Yes	Phase I	3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	N/A	Fred Hutchinson Cancer Research Centre (NCI as collaborator)	Non-for-profit	Big	2700	$ 436.550.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
102	Clinicaltrials.gov	MSC for occlusive disease of the kidney	2013	Yes	Phase I	14 Diseases of the genitourinary system	Autologous	Mayo Clinic	Non-for-profit	Big	59500	$ 9.760.600.000,00
103	Clinicaltrials.gov	Safety of autologous stem cell infusion for children with acquired hearing loss	2014	Yes	Phase I/II	8 Diseases of the ear and mastoid process	Autologous	Florida Hospital (CBR Systems Inc. as collaborator)	Non-for-profit	Big	33000	N/R
104	Clinicaltrials.gov	Immunotherapy of melanoma with tumour antigen RNA and small inhibitory RNA transfected autologous dendritic cells	2008	Yes	Phase I	2 Neoplasms	N/A	Duke University Medical Centre	Academia	Big	10024	$ 3.050.000.000,00
105	Clinicaltrials.gov	Evaluation of CureXcell® in treating chronic venous leg ulcers	2014	Yes	Phase III	9 Diseases of the circulatory system	Allogeneic	Macrocure Ltd.	Profit	Small	28	N/R
106	Clinicaltrials.gov	Long term follow-up study of human immunodefficiency virus type 1 (HIV-1) positive patients who have received OZ1 gene therapy as part of a clinical trial	2010	Yes	Phase II	1 Certain infectious and parasitic diseases	N/A	Janssen-Cilag Pty Ltd	Profit	N/R	N/R	N/R
107	Clinicaltrials.gov	Phase I dose escalation safety study of RetinoStat in advanced age-related	2011	Yes	Phase I	7 Diseases of the eye and adnexa	N/A	Oxford BioMedica	Profit	Medium	134	$ 21.186.080,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		macular degeneration (AMD)										
108	Clinicaltrials.gov	A study evaluating the safety and efficacy of the LentiGlobin BB305 drug product in severe sickle cell disease	2014	Yes	Phase I	3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	N/A	Bluebird Bio	Profit	Medium	207	$18.990.000,00
109	Clinicaltrials.gov	Stem cell gene for sickle cell disease	2014	Yes	Phase I	3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Autologous	Children's Hospital Los Angeles	Non-for-profit	Big	5276	$ 803.315.000,00
110	Clinicaltrials.gov	Her2 chimeric antigen receptor expressing T cells in advanced sarcoma	2009	Yes	Phase I	2 Neoplasms	N/A	Baylor College of Medicine	Academia	Big	8924	$ 604.276.000,00
111	Clinicaltrials.gov	Gene therapy using anti-her-2 cells treat metastatic cancer	2009	Yes	Phase I/II	2 Neoplasms	N/A	National Institutes of Health (NIH)	Non-for-profit	N/R		

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
112	Clinicaltrials.gov	Safety study of TissueGene-C in degenerative joint disease of the knee	2008	Yes	Phase I	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	TissueGene Inc.	Profit	N/R	N/R	$11.186.000,00
113	Clinicaltrials.gov	Transfer of genetically engineered lymphocytes in melanoma patients	2012	Yes	Phase I	2 Neoplasms	N/A	Loyola University (NCI as collaborator)	Academia	Big	2392	$ 559.061.000,00
114	Clinicaltrials.gov	Redirected MazF CD4 autologous T cells for HIV gene therapy	2013	Yes	Phase I	3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Autologous	University of Pennsylvania	Academia	Big	4555	$ 881.000.000,00
115	Clinicaltrials.gov	Redirected high affinity gagaspecific autologous T-cells for HIV gene therapy	2009	Yes	Phase I	3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Autologous	University of Pennsylvania	Academia	Big	4555	$ 881.000.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
116	Clinicaltrials.gov	CT antigen TCR-redirected T-cells for ovarian cancer	2012	Yes	Phase I/II	2 Neoplasms	N/R	Adaptimmune	Profit	Medium	190	$ 10.723.000
117	Clinicaltrials.gov	Anti-MART-1 F5 lymphocytes to treat high risk melanoma patients	2008	Yes	Phase II	2 Neoplasms	N/A	National Cancer Institute (NCI)	Non-for-profit	Big	4000	$ 4.950.000.000
118	Clinicaltrials.gov	IL-12 gene and in vivo electroporation-mediated plasmid DNA vaccine therapy in patients with merkel cell cancer	2011	Yes	Phase II	2 Neoplasms	N/A	OncoSec Medical Inc.	Profit	Medium	53	$ 0,0
119	Clinicaltrials.gov	Tumour infiltrating lymphocytes (TIL) transduced with TGFbDNRII	2013	Yes	Phase I	2 Neoplasms	N/A	M.D. Anderson Cancer Centre (CPRIT. as collaborator)	Non-for-profit	Big	20000	$ 4.412.923.943,00
120	Clinicaltrials.gov	TGF-beta resistant cytotoxic T-lymphocytes in treatment of EBV-positive nasopharyngeal carcinoma/RESIST-NPC	2014	Yes	Phase I	2 Neoplasms	N/A	Baylor College of Medicine	Academia	Big	8924	$ 604.276.000,00
121	Clinicaltrials.gov	Activated T lymphocytes expressing CARs, relapsed CD19+ malignancies post-allo HSCT (CARPASCIO)	2014	Yes	Phase I	2 Neoplasms	N/A	Baylor College of Medicine	Academia	Big	8924	$ 604.276.000,00
122	Clinicaltrials.gov	Administration of donor T-cells with the caspase-9 suicide gene	2011	Yes	Phase I	2 Neoplasms	N/A	Baylor College of Medicine	Academia	Big	8924	$ 604.276.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
123	Clinicaltrials.gov	Microfracture versus adipose derived stem cells for the treatment of articular cartilage defects	2014	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Stanford University	Academia	Big	2153	$ 9.051.000.000,00
124	Clinicaltrials.gov	Investigation of A-ECM for the correction of soft tissue defects	2013	Yes	Phase I	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	Aegeria SoftTissue LLC	Profit	N/R	N/R	N/R
125	Clinicaltrials.gov	Lymphodepletion plus adoptive cell transfer with high dose IL-2 in patients with metastatic melanoma	2009	Yes	Phase I/II	2 Neoplasms	Autologous	H. Lee Moffitt Cancer Centre and Research Institute	Non-for-profit	Big	4500	$ 951.032.045,00
126	CIRM	Autologous dendritic cell-tumour cell imunotherapy for metastatic melanoma	2013	Yes	Phase III	2 Neoplasms	Autologous	Caladrius Biosciences, Inc.	Profit	Medium	182	$17.900.000,00
127	CIRM	Allogeneic heart stem cells to achieve myocardial regeneration (ALL STAR)	2012	Yes	Phase II	9 Diseases of the circulatory system	Allogeneic	Capricor Inc.	Profit	Small	28	$ 4.787.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
128	CIRM	Safety study of a dual anti-HIV gene transfer construct to treat HIV-1 infection	2013	Yes	Phase I/II	3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	N/A	Calimmune, Inc.	Profit	N/R	N/R	N/R
129	CIRM	Stem cell gene therapy for sickel cell disease	2014	Yes	Phase I	3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Autologous	University of California, Los Angeles	Academia	Big	32110	$ 4.930.000.000,00
130	CIRM	A safety, tolerability, and efficacy study of VC-01 combination product in subjects with type I diabetes mellitus	2014	Yes	Phase I/II	4 Endocrine, nutritional and metabolic diseases	N/A	Viacyte Inc	Profit	Medium	51-200	N/R
131	CIRM	Safety study on GRNOPC1 in spinal cord injury	2010	Yes	Phase I	13 Diseases of the musculoskeletal system and connective tissue	N/R	Asterias Biotherapeutics, Inc.	Profit	Small	25	$ 4.030.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
132	CIRM	Study of Gene Modified Immune Cells in Patients With Advanced Melanoma (F5)	2009	Yes	Phase II	2 Neoplasms	N/A	Jonsson Comprehensive Cancer Centre	Academia	Medium	230	$ 10.380.271,00

Table A7.2 Clinical trials of advanced therapies in CA

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
	Database	*Description of the researched product*	*Research year*	*Tested in humans or not*	*Preclinical-Phase III*	*High level categorisation (ICD-10)*	*Autologous or Allogeneic*	*Organisation developing product*	*Profit, non-for-profit, academia*	*Small 0-50 employees, medium 50-250, big >250*	*Number of employees*	*US$*
1	PubMed/EMBASE	Prospective study on the treatment of lower-extremity chronic venous and mixed ulcers using tissue-engineered skin substitute made by the self-assembly approach	2013	Yes	Phase I	12 Diseases of the skin and subcutaneous tissue	Allogeneic	Quebec CHU	Non-for-profit	Big	14400	$ 1.064.795.791,64
2	PubMed/EMBASE	Effect of alipogene tiparvovec (AAV1-LPL(S447X)) on postprandial chylomicron metabolism in lipoprotein lipase-deficient patients	2012	Yes	Phase I	4 Endocrine, nutritional and metabolic diseases	N/A	UniQure (Glybera)	Profit	Medium	51-200 (linkedin)	$ 5.713.790,00
3	PubMed/EMBASE	Autologous muscle derived cell therapy for stress urinary incontinence: a prospective, dose ranging study	2013	Yes	Phase III	14 Diseases of the genitourinary system	Autologous	Cook MyoSite	Profit	Medium	Medium	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
4	PubMed/EMBASE	Development, characterization and clinical use of a biodegradable composite scaffold for bone engineering in oro-maxillo-facial surgery	2010	Yes	Phase I	17 Congenital malformations, deformations and chromosomal abnormalities	Autologous (migrating cells)	University of Toronto, department Dentistry	Academia	Big	19850	$ 2.334.024.240,00
5	PubMed/EMBASE	Efficacy and long-term safety of alipogene tiparvovec (AAV1-LPLS447X) gene therapy for lipoprotein lipase deficiency: an open-label trial	2013	Yes	Phase I	4 Endocrine, nutritional and metabolic diseases	N/A	UniQure (Glybera)	Profit	Medium	51-200 (linkedin)	$ 5.713.790,00
6	PubMed/EMBASE	Allogeneic human mesenchymal stem cell therapy (remestemcel-L, Prochymal) as a rescue agent for severe refractory acute graft-versus-host disease in pediatric patients	2014	Yes	Phase I	3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Allogeneic	Osiris Therapeutics	Profit	Medium	211	$ 86.600.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
7	PubMed/EMBASE	One-year safety analysis of the COMPARE-AMI trial: Comparison of intracoronary injection of CD133+ bone marrow stem cells to placebo in patients after acute myocardial infarction and left ventricular dysfunction	2011	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Centre Hospitalier de l'Universite de Montreal (CHUM)	Academia	Big	5910	
8	PubMed/EMBASE	Stem Cell Therapy for the Broken Heart: Mini-Organ Transplantation	2009	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	Centre Hospitalier de l'Universite de Montreal (CHUM)	Academia	Big	5910	
9	PubMed/EMBASE	COMPARE-AMI trial: comparison of intracoronary injection of CD133+ bone marrow stem cells to placebo in patients after acute myocardial infarction and left ventricular dysfunction: study	2010	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Centre Hospitalier de l'Universite de Montreal (CHUM)	Academia	Big	5910	

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		rationale and design										
10	PubMed/EMBASE	VEGF gene therapy fails to improve perfusion of ischemic myocardium in patients with advanced coronary disease: Results of the NORTHERN trial	2009	Yes	Phase II	9 Diseases of the circulatory system	N/A	St. Michaels Hospital Toronto (funds from Canadian Institute of Health Research & Heart and Stroke Foundation of Ontario)	Non-for-profit	Big	8152	$ 556.155.209,20
11	PubMed/EMBASE	Rationale and design of Enhanced Angiogenic Cell Therapy in Acute Myocardial Infarction (ENACT-AMI): The first randomized placebo-controlled trial of enhanced progenitor cell therapy for acute myocardial infarction	2010	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Ottawa Hospital Research Institute	Non-for-profit	Big	1727	$ 93.698.560,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
12	Clinicaltrials.gov	Retinal Gene Therapy for Choroideremia Using an Adeno-associated Viral Vector (AAV2) Encoding Rab-escort Protein-1 (REP1)	2014	Yes	Phase I/II	7 Diseases of the eye and adnexa	N/A	University of Alberta	Academia	Big	11000	$ 1.576.684.960,00
13	Clinicaltrials.gov	A study of the efficacy and safety of ABH001 in the treatment of patients with epidermolysis bullosa who have wounds that are not healing	2012	Yes	Phase III	17 Congenital malformations, deformations and chromosomal abnormalities	Allogeneic	Shire Regenerative Medicine Inc.	Profit	Big	5300 (2014)	$4.757.000,00
14	Clinicaltrials.gov	Autologous cell therapy for female stress urinary incontinence	2009	Yes	Phase II	14 Diseases of the genitourinary system	Autologous	Cook MyoSite Inc.	Profit	Medium	Medium	N/R
15	Clinicaltrials.gov	The enhanced angiogenic cell therapy- acute myocardial infarction trial (ENACT-AMI)	2009	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Ottawa Hospital Research Institute	Non-for-profit	Big	1727	$ 93.698.560,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
16	Clinicaltrials.gov	Autlogous cell therapy for ischemic heart failure	2011	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	Cook MyoSite Inc.	Profit	Medium	Medium	N/R
17	Clinicaltrials.gov	Autologous cell therapy for treatment of fecal incontinence	2012	Yes	Phase I/II	18 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	Autologous	Cook MyoSite Inc.	Profit	Medium	Medium	N/R
18	Clinicaltrials.gov	Safety and efficacy of intravenous autologous mesenchymal stem cells for mutltiple sclerosis: a phase 2 proof of concept study (MESCAMS)	2014	Yes	Phase II	6 Diseases of the nervous system	Autologous	Ottawa Hospital Research Institute	Non-for-profit	Big	1727	$ 93.698.560,00
19	Clinicaltrials.gov	Autologous muscle-derived cells female stress urinary incontinence clinical study	2011	Yes	Phase III	14 Diseases of the genitourinary system	Autologous	Cook MyoSite Inc.	Profit	Medium	Medium	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
20	Clinicaltrials.gov	A clinical study to assess blood-borne autologous angiogenic cell precrursors therapy in patients with critical limb ischemia	2014	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Hemostemix	Profit	Small	1-10 (Linkedin)	$ 0,00
21	Clinicaltrials.gov	An investigation on the safety of 4 different doses of autologous muscle derived cells as a therapy for stress urinary incontinence	2009	Yes	Phase II	14 Diseases of the genitourinary system	Autologous	Cook MyoSite Inc.	Profit	Medium	Medium	N/R
22	Clinicaltrials.gov	An efficacy, safety and tolerability study of Ixmyelocel-T administered via transendocardial catheter-based injections to subjects with heart failure due to ischemic dilated cardiomyopathy (IDCM)	2012	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Vericel Corporation	Profit	Medium	187	$ 50.450.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
23	Clinicaltrials.gov	IMPACT-CABG trial: implantation of autologous CD133+ stem cells in patients undergoing CABG	2009	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Centre Hospitalier de l'Universite de Montreal (CHUM) (Miltenyi Biotec Inc. as collaborator)	Non-for-profit	Big	5910	
24	Clinicaltrials.gov	Safety study of VCT-01 in split-thickness skin graft donor site wounds	2011	Yes	N/R	19 Injury, poisoning and certain other consequences of external causes	N/R	Organogenesis Inc.	Profit	Big	600	$100.000.000,00
25	Clinicaltrials.gov	An open label clinical trial of retinal gene therapy for choroideremia	2014	Yes	Phase I/II	7 Diseases of the eye and adnexa	N/A	University of Alberta	Academia	Big	11000	$ 1.576.684.960,00
26	Clinicaltrials.gov	Duration of effect of allipogene tiparvovec treatment, which was administered in other studies	2011	Yes	Phase I/II	4 Endocrine, nutritional and metabolic diseases	N/A	Amsterdam Molecular Therapeutics	Profit	N/R		

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
27	cancerview.ca	A phase I/II study of MG1 Maraba/MAGE-A3 (MG1MA3), with and without adenovirus vaccine, with transgenic MAGE-A3 insertion (AdMA3) in patients with incurable advanced/metastatic MAGE-A3-expressing solid tumours	2014	Yes	Phase I/II	2 Neoplasms	N/A	Ottawa Hospital Research Institute	Non-for-profit	Big	1727	$ 93.698.560,00
28	cancerview.ca	Retrospective analysis of treatment outcomes of allogeneic stem cell transplantation for chronic myeloid leukemia after TKI failure	2014	Yes	Phase II/III	2 Neoplasms	Allogeneic	University Health Network Toronto	Non-for-profit	Big	16149	$ 1.739.928.864,80
29	cancerview.ca	Mismatched donor cells to treat acute myeloid leukemia (ATAC-AML-01)	2013	Yes	Phase I/II	2 Neoplasms	Allogeneic	Maisonneuve -Rosemont Hospital	Non-for-profit	Big	5444	

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
30	cancerview.ca	Tumour-infiltrating lymphocytes and low-dose interleukin-2 therapy following cyclophosphamide and fludarabine in patients with melanoma	2013	Yes	Phase II	2 Neoplasms	Autologous	University Health Network Toronto	Non-for-profit	Big	16149	$ 1.739.928.864,80
31	cancerview.ca	Re-Stimulated" Tumour-Infiltrating Lymphocytes And Low-Dose Interleukin-2 Therapy in Patients With Platinum Resistant High Grade Serous Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	2013	Yes	Phase I	2 Neoplasms	Autologous	University Health Network Toronto	Non-for-profit	Big	16149	$ 1.739.928.864,80
32	cancerview.ca	Zevalin With Non Myeloablative Allogeneic Stem Cell Transplantation in Patients With Non Hodgkin Lymphoma	2008	Yes	Phase I/II	2 Neoplasms	Allogeneic	Maisonneuve -Rosemont Hospital	Non-for-profit	Big	5444	

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
33	University of Toronto	IMPACT-CABG trial: implantation of autologous CD133+ stem cells in patients undergoing CABG	2009	Yes	Phase II	9 Diseases of the circulatory system	Autologous	University Health Network, Toronto	Non-for-profit	Big	16149	$ 1.739.928.864,80
34	Faculté de médecine de l'Université Laval	Autologous Cultured Corneal Epithelium (CECA) for the Treatment of Limbal Stem Cell Deficiency	2012	Yes	Phase I/II	19 Injury, poisoning and certain other consequences of external causes	Autologous	Quebec CHU	Non-for-profit	Big	14400	$ 1.064.795.791,64
35	Office of Patented Medicines & Liaison, CIRM (involved)	A phase i/ii study of the safety and preliminary efficacy of intramedullary spinal cord transplantation of human cns stem cells (hucns-sc) in subjects with thoraic (t2-t11) spinal cord trauma."	2011	Yes	Phase I/II	19 Injury, poisoning and certain other consequences of external causes	Allogeneic	Stemcells Inc.	Profit	Medium	69	$ 971.080,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
36	Office of Patented Medicines & Liaison	A prospective, randomized, double-blinded, active-control and unblinded standard of care (soc) controlled study to determine the efficacy and safety of targeted intramyocardial delivery of autologous cd34+cells (auto-cd34+cells) for increasing exercise capacity during standardized exercise testing in subjects with refractory angina pectoris and chronic myocardial ischemia (cmi).	2012	Yes	Phase III	9 Diseases of the circulatory system	autologous	Baxter Healthcare Corporation	Profit	Big	61500	$ 14.967.000.000,00
37	Office of Patented Medicines & Liaison	A double-blind, randomized, sham-procedure-controlled, parallel	2014	Yes	Phase III	9 Diseases of the circulatory system	Allogeneic	Teva Branded Pharmaceutical Products	Profit	Big	46000 (2012)	$ 19.940.000.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		group efficacy and safety study of allogenic mesenchymal precusor cells (cep-41750) in patients with chronic heart failure due to left ventricular systolic dysfunction of either ischemic or nonischemic etiology						R&D Inc				
38	Office of Patented Medicines & Liaison	A prospective, multicentre, open-label, first-in-human phase 1/2 study with two cohorts to evaluate the safety, tolerability, and efficacy of various doses of vc-01 combination product in subjects with type 1 diabetes mellitus	2014	Yes	Phase I/II	4 Endocrine, nutritional and metabolic diseases	N/A	Viacyte Inc	Profit	Medium	51-200	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
39	Office of Patented Medicines & Liaison	Randomized, double-blind, placebo-controlled phase i/ii study of the safety and efficacy of intracoronary delivery of allogeneic cardiosphere-derived cells in patients with a myocardial infarction and ischemic left ventricular dysfunction (allogenic heart stem cells to achieve myocardial regeneration. Allstar)	2012	Yes	Phase I/II	9 Diseases of the circulatory system	Allogeneic	Capricor Inc	Profit	Small	28	$ 4.787.000,00

Table A7.3 Clinical trials of advanced therapies in JP

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
	Database	*Description of the researched product*	*Research year*	*Tested in humans or not*	*Preclinical-Phase III*	*High level categorisation (ICD-10)*	*Autologous or Allogeneic*	*Organisation developing product*	*Profit, non-for-profit, academia*	*Small 0-50 employees, medium 50-250, big >250*	*Number of employees*	*US$*
1	PubMed/ EMBASE	Cultured autologous oral mucosal epithelial cell sheet (CAOMECS) transplantation for the treatment of corneal limbal epithelial stem cell deficiency	2012	Yes	Phase I/II	7 Diseases of the eye and adnexa	Autologous	Hospital Edouard Herriot (supported by CellSeed Inc. but not directly involved in clinical trial)	Non-for-profit	Big	23000	$ 1.945.120.000,00
2	PubMed/ EMBASE	Gene therapy for parkinson's disease	2011	N/R	N/R	5 Mental and behavioural disorders	N/R	N/R	N/R	N/R	N/R	N/R
3	PubMed/ EMBASE	Clinical impact of combined transplantation of autologous skeletal myoblasts and bone marrow mononuclear cells in patients with severely deteriorated ischemic cardiomyopathy	2011	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Osaka University	Academia	Big	6363	$ 1.206.626.400.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
4	PubMed/ EMBASE	Phase II clinical trial of CD34+ cell therapy to explore endpoint selection and timing in patients with critical limb ischemia	2014	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Institute of Biomedical Research and Innovation, Kobe	Non-for-profit	Big	5633	$ 69.081.600,00
5	PubMed/ EMBASE	Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke	2011	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Sapporo Medical University	Academia	Big	201-500 employees	$ 11.102.607,60
6	PubMed/ EMBASE	Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus	2013	Yes	Phase II	4 Endocrine, nutritional and metabolic diseases	Allogeneic	Affiliated Hospital of Medical College Qingdao (CHINA)	Non-for-profit/academia	Big	2300	N/R
7	PubMed/ EMBASE	Autologous bone-marrow mononuclear cell implantation reduces long-term major amputation risk in patients with critical limb ischemia: a comparison of atherosclerotic	2011	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Graduate School of Biomedical Sciences Hiroshuma University	Academia	Medium	307	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		peripheral arterial disease and Buerger disease										
8	PubMed/ EMBASE	Impact of implanted bone marrow progenitor cell composition on limb salvage after cell implantation in patients with critical limb ischemia	2010	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Showa University School of Medicine	Academia	Medium	240	$ 1.231.358.641,04
9	PubMed/ EMBASE	Transplantation of tissue-engineered cartilage for the treatment of osteochondritis dissecans in the elbow: outcomes over a four-year follow-up in two patients	2010	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Hokkaido University School of Medicine, Sapporo	Academia	Big	4441	$ 798.537.600,00
10	PubMed/ EMBASE	A tissue-engineering approach for stenosis of the trachea and/or cricoid	2010	Yes	Phase I/II	10 Diseases of the respiratory system	Allogeneic (use of porcine skin)	Medical Research Institute, Kitano Hospital, Osaka	Non-for-profit	Big	1000	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
11	PubMed/ EMBASE	Regenerative treatment for tympanic membrane perforation	2011	Yes	Phase II	8 Diseases of the ear and mastoid process	Endogenously	Medical Research Institute, Kitano Hospital, Osaka	Non-for-profit	Big	1000	N/R
12	PubMed/ EMBASE	Improvement of eustachian tube function by tissue-engineered regeneration of mastoid air cells	2013	Yes	Phase II	8 Diseases of the ear and mastoid process	Autologous	Medical Research Institute, Kitano Hospital, Osaka	Non-for-profit	Big	1000	N/R
13	PubMed/ EMBASE	Intramuscular transplantation of G-CSF-mobilized CD34+ cells in patients with critical limb ischemia: A phase I/IIa, multicentre, single-blinded, dose-escalation clinical trial	2009	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	Institute of Biomedical Research and Innovation, Kobe	Non-for-profit	Big	5633	$ 69.081.600,00
14	PubMed/ EMBASE	Long-term clinical outcome after intramuscular transplantation of granulocyte colony stimulating factor-mobilized CD34 positive cells in patients with	2012	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	Institute of Biomedical Research and Innovation, Kobe	Non-for-profit	Big	5633	$ 69.081.600,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		critical limb ischemia										
15	PubMed/ EMBASE	Local transplantation of granulocyte colony stimulating factor-mobilized CD34+ cells for patients with femoral and tibial nonunion: Pilot clinical trial	2014	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Graduate School of Medicine, Kobe	Academia	Big	2580	$ 596.937.600,00
16	PubMed/ EMBASE	Long-term follow-up evaluation of results from clinical trial using hepatocyte growth factor gene to treat severe peripheral arterial disease	2012	Yes	Phase I/II	9 Diseases of the circulatory system	N/R	Osaka University	Academia	Big	6363	$ 1.206.626.400.000,00
17	PubMed/ EMBASE	Long-term clinical outcome after intramuscular implantation of bone marrow mononuclear cells (Therapeutic Angiogenesis by Cell Transplantation [TACT] trial) in patients with chronic limb ischemia	2008	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Kyoto Prefectural University of Medicine	Academia	Medium	153	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
18	PubMed/ EMBASE	Phase I/IIa clinical trial of therapeutic angiogenesis using hepatocyte growth factor gene transfer to treat critical limb ischemia	2011	Yes	Phase I/II	9 Diseases of the circulatory system	N/R	Osaka University	Academia	Big	6363	$ 1.206.626.400.000,00
19	PubMed/ EMBASE	A clinical study of alveolar bone tissue engineering with cultured autogenous periosteal cells: coordinated activation of bone formation and resorption	2012	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Niigata University Graduate School of Medical and Dental Sciences	Academia	Big	2420	$ 710.937.500,00
20	PubMed/ EMBASE	Long-term phenotypic study after allogeneic cultivated corneal limbal epithelial transplantation for severe ocular surface diseases	2010	Yes	Phase I/II	7 Diseases of the eye and adnexa	Allogeneic	Kyoto Prefectural University of Medicine	Academia	Medium	153	N/R
21	PubMed/ EMBASE	Establishment of culturing system for ex-vivo expansion of angiogenic immature erythroid cells, and its application for treatment of patients with chronic	2010	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Niigata University Graduate School of Medical and Dental Sciences	Academia	Big	2420	$ 710.937.500,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		severe lower limb ischemia										
22	PubMed/ EMBASE	Tissue-engineered cultured periosteum sheet application to treat infrabony defects: case series and 5-year results	2013	Yes	Phase I/II	2 Neoplasms	Autologous	Niigata University Graduate School of Medical and Dental Sciences	Academia	Big	2420	$ 710.937.500,00
23	PubMed/ EMBASE	Clinical application of in situ tissue engineering using a scaffolding technique for reconstruction of the larynx and trachea	2008	Yes	Phase I/II	10 Diseases of the respiratory system	Allogeneic (porcine collagen)/autologous (venous blood)	Fukushima Medical University	Academia	Big	1527	N/R
24	PubMed/ EMBASE	Allogeneic hematopoietic stem cell transplantation for patients with mildly reduced renal function as defined based on creatinine clearance before transplantation	2013	Yes	Phase II/III	14 Diseases of the genitourinary system	Allogeneic	Jichi Medical University	Academia	Big	4160	N/R
25	PubMed/ EMBASE	Impact of enzyme replacement therapy and hematopoietic stem cell therapy on growth in patients with Hunter	2014	Yes	Phase II	4 Endocrine, nutritional and metabolic diseases	Allogeneic	duPont Hospital for Children/Gifu University	Non-for-profit	Big	2027	$ 319.477.200,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		syndrome										
26	PubMed/ EMBASE	Tissue engineered myoblast sheets improved cardiac function sufficiently to discontinue LVAS in a patient with DCM: report of a case	2012	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Osaka University	Academia	Big	6363	$ 1.206.626.400.000,00
27	PubMed/ EMBASE	Gene therapy for esophageal squamous cell carcinoma	2008	Yes	Phase I/II	2 Neoplasms	N/R	Chiba University Graduate School of Medicine	Academia	Medium	170	$ 584.539.200,00
28	PubMed/ EMBASE	Long-term follow-up of cultured epidermal autograft in a patient with recessive dystrophic epidermolysis bullosa	2014	Yes	Phase I	17 Congenital malformations, deformations and chromosomal abnormalities	Autologous	Hokkaido University School of Medicine, Sapporo	Academia	Big	4441	$ 798.537.600,00
29	PubMed/ EMBASE	Ocular surface reconstruction using the combination of autologous cultivated oral mucosal epithelial transplantation and eyelid surgery for severe ocular surface disease	2011	Yes	Phase I/II	7 Diseases of the eye and adnexa	Autologous	Kyoto Prefectural University of Medicine	Academia	Medium	153	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
30	PubMed/ EMBASE	Autologous G-CSF-mobilized peripheral blood CD34+ cell therapy for diabetic patients with chronic nonhealing ulcer	2014	Yes	Phase I/II	12 Diseases of the skin and subcutaneous tissue	Autologous	Juntendo University School of Medicine	Academia	Big	3812	$ 1.241.000.000,00
31	PubMed/ EMBASE	Atelocollagen-associated autologous chondrocyte implantation for the repair of chondral defects of the knee: a prospective multicentre clinical trial in Japan	2009	Yes	Phase II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Hokkaido University School of Medicine, Sapporo	Academia	Big	4441	$ 798.537.600,00
32	PubMed/ EMBASE	Effective treatment of intractable skin ulcers using allogeneic cultured dermal substitutes in patients with systemic lupus erythematosus	2009	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	Wakayama Medical University	Academia	N/R	N/R	N/R
33	PubMed/ EMBASE	Sprayed cultured mucosal epithelial cell for deep dermal burns	2010	Yes	Phase I/II	19 Injury, poisoning and certain other consequences of external causes	Autologous	Nagoya University	Academia	Big	3638	$ 948.553.200,00
34	PubMed/ EMBASE	Injectable bone applied for ridge augmentation and dental implant	2008	Yes	Phase I/II	11 Diseases of the digestive system	Autologous	Nagoya University	Academia	Big	3638	$ 948.553.200,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		placement: human progress study										
35	PubMed/ EMBASE	Minimally invasive approach with tissue engineering for severe alveolar bone atrophy case	2013	Yes	Phase I	11 Diseases of the digestive system	Autologous	Nagoya University	Academia	Big	3638	$ 948.553.200,00
36	PubMed/ EMBASE	Injectable tissue-engineered bone using autogenous bone marrow-derived stromal cells for maxillary sinus augmentation: clinical application report from a 2-6-year follow-up	2008	Yes	Phase II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Nagoya University	Academia	Big	3638	$ 948.553.200,00
37	PubMed/ EMBASE	Tissue-engineered cultured periosteum used with platelet-rich plasma and hydroxyapatite in treating human osseous defects	2008	Yes	Phase I/II	11 Diseases of the digestive system	Autologous	Niigata University Graduate School of Medical and Dental Sciences	Academia	Big	2420	$ 710.937.500,00
38	PubMed/ EMBASE	Two-stage transplantation of cell-engineered autologous auricular chondrocytes to regenerate chondrofat	2013	Yes	Phase I/II	17 Congenital malformations, deformations and chromosomal	Autologous	Osaka City General Hospital & Kagawa University	Non-for-profit	Big	1189	$ 324.059.047,20

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		composite tissue: clinical application in regenerative surgery				abnormalities		Faculty of Medicine				
39	PubMed/ EMBASE	Wound therapy by marrow mesenchymal cell transplantation	2008	Yes	Phase I/II	19 Injury, poisoning and certain other consequences of external causes	Autologous	Nara Medical University	Academia	N/R	N/R	N/R
40	PubMed/ EMBASE	Transfection of human HGF plasmid DNA improves limb salvage in Buerger's disease patients with critical limb ischemia	2011	Yes	Phase I/II	9 Diseases of the circulatory system	N/R	Tokyo Medical University	Academia	Big	3950	N/R
41	Clinicaltrials.gov	Transcoronary infusion of cardiac progenitor cells in patients with single ventricle physiology	2011	Yes	Phase I	17 Congenital malformations, deformations and chromosomal abnormalities	Autologous	Okayama University (National Cerebral and Cardiovascular Centre as collaborator)	Academia	Big	2647	$ 555.937.200,00
42	Clinicaltrials.gov	Clinical trial of autologous adipose tissue derived stromal cell therapy for ischemic heart failure	2012	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	Kanazawa University	Academia	Big	2709	$ 469.257.600,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
43	Clinicaltrials.gov	Gene therapy for B-cell non-hodgkin lymphona using CD19 CAR gene transduced T-lymphocytes	2014	Yes	Phase I/II	2 Neoplasms	N/A	Jichi Medical University (Takara Bio Inc. as collaborator)	Academia	Big	4160	N/R
44	Clinicaltrials.gov	Autologous human cardiac -derived stem cell to treat ischemic cardiomyopathy (ALCADIA)	2009	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Asahikawa Medical College (also in collaboration with National cerebral and cardiovascular centre translational research informatics centre)	Academia	Big	1025	N/R
45	Clinicaltrials.gov	Investigator initiated phase I study of TBI-1201	2014	Yes	Phase I	2 Neoplasms	N/A	Mie University (Takara Bio Inc, Shionogi, Fiverings Co. & Statcom Co. as collaborators)	Academia	Big	1877	$ 345.744.000,00
46	Clinicaltrials.gov	Safety study of liver regeneration therapy using cultured	2014	Yes	Phase I	11 Diseases of the digestive system	Autologous	Yamaguchi University Hospital	Non-for-profit	Big	1500	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		autologous BMSCs										
47	Clinicaltrials.gov	Randomized phase II b trial of DVC1-0101	2014	Yes	Phase II	9 Diseases of the circulatory system	N/A	Kyushu University (CPC Clinical Research Collorado, Iberica Co & Ministry of Health as collaborators)	Academia	Big	5084	$ 970.981.200,00
48	UMIN	Healing acceleration of repaired meniscus by synovial stem cells Clinical study to assess the safety and efficacy of transplantation of autologous synovial mesenchymal stem cells in patients with knee meniscal tear.	2013	Yes	Phase I/II	19 Injury, poisoning and certain other consequences of external causes	Autologous	Medical Hospital of Tokyo Medical and Dental University	Academia	Big	1279	$ 272.812.663,20
49	JMACCT	Study of Breast Reconstruction with Adipose tissue-derived mesenchymal stem cells (ADSCs) in the Treatment of Patients with Breast Deformities Post-breast	2014	Yes	Phase I/II	14 Diseases of the genitourinary system	N/R	Rie Yamashita	N/R	N/R	N/R	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		Conservation Therapy										
50	UMIN	Clinical application of corneal endothelial regenerative medicine by means of cultured human corneal endothelial cell transplantation	2013	Yes	Phase I/II	7 Diseases of the eye and adnexa	N/R	Kyoto Prefectural University of Medicine	Academia	Medium	153	N/R
51	JMACCT	Intravenous infusion of autologous mesenchymal stem cells from bone marrow for spinal cord injury patients: open label clinical trial (exploratory trial)	2014	Yes	Phase II	19 Injury, poisoning and certain other consequences of external causes	Autologous	Toshihiko Yamashita, MD, PhD	N/R	N/R	N/R	N/R
52	UMIN	Bone regenerative medicine using allogeneic bone marrow derived mesenchymal stem cells secretome	2013	Yes	Phase II	11 Diseases of the digestive system	Allogeneic	Nagoya University Hospital	Academia	Big	2042	$ 279.812.400,00
53	UMIN	Safety investigations for the bone regenerative medicine using growth factors secreted from the patients' own stem cells	2013	Yes	Phase I	11 Diseases of the digestive system	Allogeneic	Nagoya University Hospital	Academia	Big	2042	$ 279.812.400,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
54	JMACCT	Intravenous infusion of autologous mesenchymal stem cells from bone marrow for stroke patients: double-blind randomized clinical trial (confirmatory trial)	2013	Yes	Phase III	9 Diseases of the circulatory system	Autologous	Osamu Honmou, MD, PhD	N/R	N/R	N/R	N/R
55	JMACCT	Intravenous infusion of autologous mesenchymal stem cells from bone marrow for stroke patients: Single arm open-label trial	2013	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Osamu Honmou, MD, PhD	N/R	N/R	N/R	N/R
56	UMIN	Transplantation of autologous mononuclear cells in patients with critical limb ischemia (CLI)	2011	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	Regenerative Medicine Unit, Division of Vascular Regeneration Therapy, Institute of Biomedical Research and Innovation (IBRI)	Non-for-profit	Big	5633	$ 69.081.600,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
57	UMIN	Transplantation of autologous and G-CSF mobilized mononuclear cells in patients with critical limb ischemia (CLI)	2012	Yes	Phase I/II	9 Diseases of the circulatory system	Autologous	Regenerative Medicine Unit, Division of Vascular Regeneration Therapy, Institute of Biomedical Research and Innovation (IBRI)	Non-for-profit	Big	5633	$ 69.081.600,00
58	UMIN	Transcoronary Infusion of Cardiac Progenitor Cells in Patients with Single Ventricle Physiology (TICAP)	2011	Yes	Phase I/II	17 Congenital malformations, deformations and chromosomal abnormalities	Autologous	Centre for Innovative Clinical Medicine, Okayama University Hospital	Academia	Big	949	$ 257.754.000,00
59	UMIN	Allogeneic Bone Marrow and Mesenchymal Stem Cell Transplantation for patients with severe Hypophosphatasia	2010	Yes	Phase I/II	4 Endocrine, nutritional and metabolic diseases	Allogeneic	Shimane University School of Medicine	Academia	Big	1920	$ 284.440.800,00
60	JMACCT	Stem cell transplantation for vascular regeneration in the legs	2008	Yes	Phase I/II	9 Diseases of the circulatory system	N/R	Atsuhiko Kawamoto	Non-for-profit	Big	5633	$ 69.081.600,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
61	UMIN	Clinical study of the efficacy of cell-based immunotherapy for malignant tumours (Observational study)	2011	Yes	N/R	2 Neoplasms	N/R	Centre for Advanced Medical Innovation, Kyushu University	Academia	Big	5084	$ 970.981.200,00
62	UMIN	Safety of cell immunotherapy for refractory malignant tumour using natural killer cell-like effector cells (CA-MED-NK001) selectively amplified from autologous mononuclear cells in peripheral blood	2014	Yes	Phase I	2 Neoplasms	Autologous	Centre for Advanced Medical Innovation, Kyushu University	Academia	Big	5084	$ 970.981.200,00
63	UMIN	Clinical Research of gene therapy for relapsed or refractory B-cell Non-Hodgkin Lymphoma using autologous T cells expressing a chimeric antigen receptor specific to the CD19 antigen	2014	Yes	Phase I	2 Neoplasms	Autologous	Jichi Medical University	Academia	Big	4160	N/R
64	UMIN	A pilot feasibility and safety study of autologous umbilical cord blood cell therapy	2014	Yes	Phase I	16 Certain conditions originating in de perinatal	Autologous	Neonatal Encephalopathy Consortium, Japan	N/R	N/R	N/R	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		in infants with neonatal encephalopathy				period						
65	UMIN	Retrospective clinical study of gynecology Cancer Immuno-Cell Therapy study group	2014	Yes	Phase II	2 Neoplasms	N/R	Juntendo University Hospital Department of Obstetrics and Gynecology	Academia	N/R	N/R	N/R
66	UMIN	Safety, efficacy and immunogenicity of concomitant molecular target drug or cytokine therapy and autologous tumour lysate-pulsed dendritic cell therapy in patients with advanced renal cell carcinoma	2014	Yes	Phase I/II	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00
67	UMIN	The evaluation for safety and efficacy of combination therapy of adoptive immune-cell therapy with chemoradiotherapy for locally advanced esophageal cancer	2014	Yes	Phase I	2 Neoplasms	N/R	Gunma University	Academia	Big	2344	$ 388.481.478,00
68	UMIN	Clinical study of combination therapy of adoptive immune-cell	2014	Yes	Phase I/II	2 Neoplasms	N/R	Gunma University	Academia	Big	2344	$ 388.481.478,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		therapy with chemoradiothrapy for pancreatic cancer										
69	UMIN	Study of immuno-Cell therapy for advanced and recurrent gastrointestinal and Hepato-biliary-pancreatic carcinoma	2014	Yes	Phase II	2 Neoplasms	N/R	Toho University	Academia	Big	4065	N/R
70	UMIN	OCV-C01 as a combination therapy of peptide-based cancer vaccines for patients with advanced biliary tract cancer refractory to priortherapy: Phase II study	2014	Yes	Phase II	2 Neoplasms	N/R	Kyushu University Hospital	Academia	Big	2852	$ 282.206.400,00
71	UMIN	Clinical study of combination therapy of adoptive immunotherapy with proton therapy for pancreatic cancer	2013	Yes	Phase I/II	2 Neoplasms	N/R	Hyogo Ion Beam Medical Centre	N/R	N/R	N/R	N/R
82	UMIN	A multi-centre double-blind parallel-group placebo-control Phase II study on the efficacy of survivin-2B peptide vaccine therapy for	2013	Yes	Phase II	2 Neoplasms	N/R	Sapporo medical university hospital	Academia	Medium	201-500 employees	$ 11.102.607,60

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		patients with advanced or recurrent pancreatic cancer, and for which there is no effective treatment										
73	UMIN	Phase I/IIa clinical study of the immunotherapy using ZNK cell for solid cancer	2013	Yes	Phase I/II	2 Neoplasms	N/R	Nagasaki University Hospital	Academia	Medium	98	$ 208.614.000,00
74	UMIN	Phase I/II clinical trial of WT1 peptide vaccine therapy for lung, breast, pancreas, stomach, and colorectal cancer	2013	Yes	Phase I/II	2 Neoplasms	N/R	Shinshu University	Academia	Big	2503	$ 408.920.400,00
75	UMIN	Clinical prospective study to investigate efficacy and safety of immune-cell therapy for malignant tumours	2013	Yes	Phase II	2 Neoplasms	N/R	Kanazawa university	Academia	Big	2709	$ 469.257.600,00
76	UMIN	Clinical trial of WT1 and MUC1 peptide-pulsed dendritic cell vaccine for post-operative patients with pancreatic cancer or biliary cancer	2013	Yes	Phase I/II	2 Neoplasms	N/R	Nagasaki University Hospital	Academia	Medium	98	$ 208.614.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
77	UMIN	Clinical trial of cellular immunotherapy for malignant tumour (cancer immunotherapy with dendritic cell-based vaccines)	2012	Yes	Phase I/II	2 Neoplasms	N/R	Centre for Advanced Medical Innovation, Kyushu University	Academia	Big	5084	$ 970.981.200,00
78	UMIN	Clinical trial of cellular immunotherapy for malignant tumour (alpha-beta T cell-based cancer immunotherapy)	2013	Yes	Phase I/II	2 Neoplasms	N/R	Centre for Advanced Medical Innovation, Kyushu University	Academia	Big	5084	$ 970.981.200,00
79	UMIN	Clinical trial of cellular immunotherapy for malignant tumour (gamma-delta T cell-based cancer immunotherapy)	2012	Yes	Phase I/II	2 Neoplasms	N/R	Centre for Advanced Medical Innovation, Kyushu University	Academia	Big	5084	$ 970.981.200,00
80	UMIN	Clinical trial of autologous adiose tissue derived stromal cell therapy for ischemic heart failure	2012	Yes	Phase I	9 Diseases of the circulatory system	Autologous	Kanazawa University	Academia	Big	2709	$ 469.257.600,00
81	UMIN	Combination of chemotherapy with docetaxel / cisplatin / fluorouracil (DCF) and autologous gamma/delta	2012	Yes	Phase I/II	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		T cell transfer therapy for esophageal cancer.										
82	UMIN	Clinical prospective study to investigate efficacy of NK cell therapy for malignant tumours.	2012	Yes	Phase I	2 Neoplasms	N/R	Seta Clinic Group	Non-for-profit	N/R	N/R	N/R
83	UMIN	Phase II study of auto-gamma/delta T cell therapy for multiple myeloma.	2012	Yes	Phase II	2 Neoplasms	N/R	Japanese Red Cross Medical Centre	Non-for-profit	N/R	N/R	N/R
84	UMIN	Phase I study of immuno-Cell therapy for advanced and recurrent esophageal squamous cell carcinoma	2012	Yes	Phase I	2 Neoplasms	N/R	Toho University	Academia	Big	4065	N/R
85	UMIN	Clinical research of bone marrow-derived mesenchymal stem cell transplantation for the patients with epidermolysis bullosa.	2011	Yes	Phase I	17 Congenital malformations, deformations and chromosomal abnormalities	N/R	Osaka University Graduate School of Medicine	Academia	Big	6363	$ 1.206.626.400.000,00
86	UMIN	Safety, efficacy and immunogenicity of concomitant interferon alpha and autologous tumour lysate-pulsed	2011	Yes	Phase I/II	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		dendritic cell therapy in patients with advanced renal cell carcinoma										
87	UMIN	Adoptive immunotherapy using zoledronate-expanded autologous gamma/delta T cells for patients with non-small cell lung cancer refractory to standard treatment.	2011	Yes	Phase II	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00
88	UMIN	Clinical study of autologous tumour lysate-pulsed dendritic cell therapy for advanced colorectal cancer (Stage3, 4)	2011	Yes	Phase I	2 Neoplasms	Autologous	Tomishiro Central Hospital	Non-for-profit	Big	1319	N/R
89	UMIN	Clinical study of autologous tumour lysate-pulsed dendritic cell therapy after resection of lung cancer	2011	Yes	Phase I	2 Neoplasms	Autologous	Seta Clinic Fukuoka	Non-for-profit	N/R	N/R	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
90	UMIN	A phase I clinical study of immune cell therapy with MAGE-A4- or Survivin-specific Th1 cells for patients with refractory virulent tumours	2011	Yes	Phase I	2 Neoplasms	N/R	Department of General Surgery, Hokkaido University Graduated School of Medicine	Academia	Big	4441	$ 798.537.600,00
91	UMIN	Clinical study to investigate recurrence efficacy on a combined use of radiofrequency ablation therapy and auto-gamma/delta T cell therapy for hepatitis C virus-related hepatocellular carcinoma patients	2010	Yes	Phase I/II	2 Neoplasms	Autologous	Tokyo Medical University	Academia	Big	3950	N/R
92	UMIN	Intraperitoneal autologous gamma/delta T cell therapy for refractory gastric cancer with ascites.	2010	Yes	Phase I	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00
93	UMIN	A phase 1 study of adoptive immunotherapy using autologous RNF43 peptide pulse dendritic cells and RNF43 peptide	2010	Yes	Phase I	2 Neoplasms	Autologous	Kyushu University Hospital	Academia	Big	2852	$ 282.206.400,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		specifically activated lymphocytes in patients with advanced solid tumours										
94	UMIN	Efficacy of adoptive cellular therapy with naive rich T cell on recurrence after curative radiofrequency ablation for primary hepatocellular carcinoma (Phase 2 study)	2010	Yes	Phase II	2 Neoplasms	N/R	Kyoto Prefectural University of Medicine, Division of Gastroenterology and Hepatology	Academia	Medium	153	N/R
95	UMIN	Clinical study to investigate safety and efficacy on a combined use of rituximab and auto-gamma/delta T cell therapy for CD20-positive B-cell lymphoma.	2010	Yes	Phase I	2 Neoplasms	Autologous	Japanese Red Cross Medical Centre	Non-for-profit	N/R	N/R	N/R
96	UMIN	Clinical study using denderitic cell vaccinations for cancer patients	2010	Yes	Phase II/III	2 Neoplasms	Autologous	Matsumoto Dental University		Big	397	N/R
97	UMIN	Safety, efficacy and immunogenicity of autologous tumour	2009	Yes	Phase I	2 Neoplasms	N/R	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		lysate-pulsed dendritic cell therapy after resection of stage2A (T2N0,T3N0) esophageal cancer										
98	UMIN	The efficacy and safety of autologous gamma/delta T cell transfer therapy after resection of stage2A (T2N0,T3N0) esophageal cancer	2009	Yes	Phase I/II	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00
99	UMIN	Randomized controlled trial of G-CSF-mobilized peripheral blood mononuclear cells transplantation for the treatment of patients with Peripheral Arterial Disease	2009	Yes	Phase II	9 Diseases of the circulatory system	N/R	Japan Study group of peripheral vascular regeneration cell therapy	N/R	N/R	N/R	N/R
100	UMIN	Safety, efficacy and immunogenicity of autologous tumour lysate-pulsed dendritic cell therapy in patients with advanced renal cell carcinoma	2009	Yes	Phase I	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
101	UMIN	Clinical trial for effectiveness and safety of WT1 peptide-pulsed allogeneic dendritic cell therapy for childhood patients with chemotherapy-resistant leukemia.	2009	Yes	Phase I	2 Neoplasms	Allogeneic	Department of Pediatrics, Shinshu University School of Medicine	Academia	Big	2503	$ 408.920.400,00
102	UMIN	The efficacy and safety of autologous gamma/delta T cell transfer therapy after resection of intrahepatic cholangiocarcinoma or biliary tract cancer	2008	Yes	Phase I/II	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00
103	UMIN	The efficacy and safety of autologous gamma/delta T cell transfer therapy for esophageal cancer	2008	Yes	Phase I/II	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00
104	UMIN	The efficacy and safety of autologous gamma/delta T cell transfer therapy for extrahepatic metastasis of hepatocellular carcinoma	2008	Yes	Phase I/II	2 Neoplasms	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
105	UMIN	Distraction osteogenesis with transplantation of culture expanded bone marrow cells	2008	Yes	Phase II	17 Congenital malformations, deformations and chromosomal abnormalities	N/R	Department of Orthopaedic Surgery, Nagoya University Hospital	Academia	Big	2042	$ 279.812.400,00
106	UMIN	A phase 2 clinical trial of a replication-competent, recombinant herpes simplex virus type 1 in patients with glioblastoma	2014	Yes	Phase II	2 Neoplasms	N/A	The IMSUT Hospital	Academia	N/R	N/R	N/R
107	UMIN	Clinical study of long-term vaccinations with MAGE-A4 peptide	2014	Yes	Phase I	2 Neoplasms	N/A	Mie University Graduate School of Medicine	Academia	Big	1877	$ 345.744.000,00
108	UMIN	Gene Therapy using Intramuscular Administration of AMG0001 in Patients with Peripheral Arterial Disease	2014	Yes	Phase I/II	9 Diseases of the circulatory system	N/A	Osaka University Hospital	Academia	Big	1325	N/R
109	UMIN	Feasibility study of the treatment of the refractory skin ulcer by the punch graft from the Natural gene therapy area in epidermolysis	2014	Yes	Phase I/II	17 Congenital malformations, deformations and chromosomal abnormalities	N/A	Hokkaido University Hospital	Academia	Big	814	$ 221.835.600,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		bullosa										
110	UMIN	A clinical study of adenovirus mediated Reduced Expression in Immortalized Cells/Dickkopf-3 (REIC/Dkk-3) gene therapy for malignant pleural mesothelioma	2014	Yes	Phase II	2 Neoplasms	N/A	Okayama University Hospital	Academia	Big	949	$ 257.754.000,00
111	UMIN	A clinical study of a replication-competent, recombinant herpes simplex virus type 1 (G47delta) in patients with progressive olfactory neuroblastoma	2013	Yes	Phase I	2 Neoplasms	N/A	IMSUT Hospital, The University of Tokyo	Academia	N/R	N/R	N/R
112	UMIN	WT1-antigen specific TCR-gene transduced T lymphocytes transfer using MS3-WT1-siTCR vector for acute myelogeneous leukemia and myelodysplastic syndrome	2013	Yes	Phase I/II	2 Neoplasms	N/A	Mie University, Ehime University, Fujita Health University, Nagoya University, Takara Bio Inc.	Academia	N/R	N/R	$ 172.737.600,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
113	UMIN	Adoptive transfer of lymphocytes transduced with MAGE-A4-specific TCR gene following lymphodepleting conditioning for therapy-resistant esophageal cancer	2013	Yes	Phase I/II	2 Neoplasms	N/A	Department of Immuno-gene Therapy, Mie University Graduate School of Medicine	Academia	Big	1877	$ 345.744.000,00
114	UMIN	The Clinical Study for Neuroprotective Gene Therapy to Treat Patients with Retinitis Pigmentosa via Subretinal Injection of The 3rd Generation of Recombinant Simian Immunodeficiency Virus (SIVagm) Vector Expressing Human Pigment Epithelium-Derived Factor (hPEDF) Gene	2013	Yes	Phase I/II	7 Diseases of the eye and adnexa	N/A	Kyushu University Hospital	Academia	Big	2852	$ 282.206.400,00
115	UMIN	A gene therapy clinical trial for chronic granulomatous disease targeting the patient's hematopoietic stem cells	2012	Yes	Phase I/II	3 Diseases of the blood and blood-forming organs and certain disorders	N/A	National Center for Child Health and Development	N/R	N/R	N/R	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
						involving the immune mechanism						
116	UMIN	Phase I study on the combination therapy of IMF-001 and MIS416 for the treatment of patients with NY-ESO-1 expressing malignant solid tumour.	2012	Yes	Phase I	2 Neoplasms	N/A	Mie University Graduate School of Medicine	Academia	Big	1877	$ 345.744.000,00
117	UMIN	Phase 1 clinical study on the combination therapy of CHP-NY-ESO-1 cancer vaccine and Poly-ICLC for the treatment of patients with NY-ESO-1 expressing refractory esophageal cancer	2012	Yes	Phase I	2 Neoplasms	N/A	Kyoto Prefectural University of Medicine	Academia	Medium	153	N/R
118	UMIN	A randomized multicenter trial of adjuvant IMF-001 after curative resection for esophageal cancer with NY-ESO-1 antigen (phase II study)	2012	Yes	Phase I/II	2 Neoplasms	N/A	Department of Immuno-gene Therapy, Mie University Graduate School of Medicine	Academia	Big	1877	$ 345.744.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
119	UMIN	MAGE-A4 peptide vaccine study after Adoptive transfer of lymphocytes transduced with MAGE-A4-specific TCR gene	2011	Yes	Phase I/II	2 Neoplasms	N/A	Mie University Graduate School of Medicine	Academia	Big	1877	$ 345.744.000,00
120	UMIN	Phase I Clinical Study on the Combination Therapy of CHP-NY-ESO-1 Cancer Vaccine and MIS416 for the Treatment of Patients with NY-ESO-1 expressing Refractory Urothelial or Prostate Cancer	2011	Yes	Phase I	2 Neoplasms	N/A	Mie University Graduate School of Medicine	Academia	Big	1877	$ 345.744.000,00
121	UMIN	A clinical study of adenovirus mediated Reduced Expression in Immortalized Cells/Dickkopf-3(REIC/Dkk-3)gene therapy for prostate cancer	2011	Yes	Phase I/II	2 Neoplasms	N/A	Okayama University hospital	Academia	Big	949	$ 257.754.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
122	UMIN	A clinical study of a replication-competent, recombinant herpes simplex virus type 1 (G47delta) in patients with progressive glioblastoma	2009	Yes	Phase I/II	2 Neoplasms	N/A	(1) The University of Tokyo Hospital (2) The IMSUT Hospital	Academia	Big	1854	$ 379.890.000,00
123	UMIN	Adoptive transfer of lymphocytes transduced with MAGE-A4-specific TCR gene for therapy-resistant esophageal cancer	2009	Yes	Phase I	2 Neoplasms	N/A	Mie University Hospital	Academia	Big	878	$ 173.602.800,00
124	UMIN	CHP-MAGE-A4 vaccine study for MAGE-A4-expressing cancer	2008	Yes	Phase I/II	2 Neoplasms	N/A	Mie University	Academia	Big	1877	$ 345.744.000,00
125	UMIN	clinical trial of CHP-HER2 cancer vaccine with immuno-adjuvant, OK-432, for advanced breast cancer	2008	Yes	Phase I/II	2 Neoplasms	N/A	Mie University, University of Ocupational and Environmental Health, Nagasaki University, National Hospital Organization Saga National	Academia	Big	1877	$ 345.744.000,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
								Hospital, Hamamatsu Medical Centre				
126	UMIN	Safety and Immunogenicity of Cholesterol-Bearing Hydrophobized Pullulan HER2 Protein 146 (CHP-HER2) and NY-ESO-1 Protein (CHP-NY-ESO-1) in Combination With OK-432 in HER2- and/or NY-ESO-1-Expressing Cancers	2008	Yes	Phase I	2 Neoplasms	N/A	Mie University Graduate School of Medicine, Kitano Hospital	Academia	Big	1877	$ 345.744.000,00
127	UMIN	Adoptive transfer of autologous T cells followed by vaccination with MAGE-A4-derived peptides after chemotherapy for MAGE-A4-expressing advanced cancer patients	2008	Yes	Phase I	2 Neoplasms	N/A	Department of Immuno-gene Therapy, Mie University Graduate School of Medicine	Academia	Big	1877	$ 345.744.000,00
128	UMIN	Long-term follow-up clinical study of cultured epithelial autografts (CEA, J-TEC-01) for patients with giant	2014	Yes	Phase I/II	2 Neoplasms	N/R	Japan Tissue Engineering Co.,Ltd	Profit	Medium	170	$ 8.467.200,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
		congenital melanocytic nevi.										
129	UMIN	A clinical study of alveolar bone tissue engineering using autologous bone marrow stromal cells	2011	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Tissue Engineering Research Group, Division of Molecular Therapy, The Advanced Clinical Research Centre, The Institute of Medical Science, The University of Tokyo	Academia	Big	7848	$ 2.054.564.400,00
130	UMIN	Clinical trial on in situ bone tissue engineering using bioactive bone substitute for acceleration of bone regeneration in sinus floor augmentation	2011	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	N/R	The Nippon Dental University, School of Life Dentistry at Tokyo Clinical study project of bone regeneration	Academia	Big	919	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication*	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual turnover
131	UMIN	Development of implant-type tissue-engineered cartilage for patients with nasal deformity in cleft lip and palate - implant-type tissue-engineered cartilage, which is made by applying autologous auricular chondrocytes to scaffolds consisting of atelocollagen hydrogel and poly-L-lactic acid (PLLA) porous body	2011	Yes	Phase I	13 Diseases of the musculoskeletal system and connective tissue	Autologous	The University of Tokyo Hospital	Academia	Big	1854	$ 379.890.000,00

Table A7.4 Clinical trials of advanced therapies in KR

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
	Database	*Description of the researched product*	*Research year*	*Tested in humans or not*	*Preclinical-Phase III*	*High level categorisation (ICD-10)*	*Autologous or Allogeneic*	*Organisation developing product*	*Profit, non-for-profit, academia*	*Small 0-50 employees, medium 50-250, big >250*	*Number of employees*	*US$*
1	PubMed/ EMBASE	Coverage of skin defects without skin grafts using adipose-derived stem cells	2013	Yes	Phase I/II	19 Injury, poisoning and certain other consequences of external causes	Autologous	University School of Medicine Gyohyeon	Academia	N/R	N/R	N/R
2	PubMed/ EMBASE	Five-year results of intracoronary infusion of the mobilized peripheral blood stem cells by granulocyte colony-stimulating factor in patients with myocardial infarction	2012	Yes	Phase II	9 Diseases of the circulatory system	Autologous	Seoul National University Hospital (sponsored by the Ministry of Health, Welfare & Family (Republic of South Korea)	Academia	Big	5944	N/R
3	PubMed/ EMBASE	Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis	2012	Yes	Phase II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Yonsei Sarang Hospital, Department of Orthopedic Surgery	N/R	Big	8191	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
4	PubMed/ EMBASE	Successful reconstruction of 15-cm segmental defects by bone marrow stem cells and resected autogenous bone graft in central hemangioma	2010	Yes	Phase III	2 Neoplasms	Autologous	Wonkwang University South Korea	Academia	N/R	N/R	N/R
5	PubMed/ EMBASE	Autologous mesenchymal stem cell therapy delays the progression of neurological deficits in patients with multiple system atrophy	2008	Yes	Phase II	6 Diseases of the nervous system	Autologous	University College of Medicine Suwon	Academia	N/R	N/R	N/R
6	PubMed/ EMBASE	Autologous adipose tissue-derived stem cells treatment demonstrated favourable and sustainable therapeutic effect for Crohn's fistula	2013	Yes	Phase II	11 Diseases of the digestive system	Autologous	Sungkyunkwan University School of Medicine Seoul	Academia	Big	5581	N/R
7	PubMed/ EMBASE	Autologous adipose tissue-derived stem cells for the treatment of Crohn's fistula: A Phase I clinical study	2012	Yes	Phase I	11 Diseases of the digestive system	Autologous	Sungkyunkwan University School of Medicine Seoul	Academia	Big	5581	N/R
8	PubMed/ EMBASE	Clinical trial of autologous differentiated adipocytes from stem cells derived from human adipose tissue	2011	Yes	Phase II	19 Injury, poisoning and certain other consequences of external causes	Autologous	Anterogen, Sungkyunkwan University, School of Medicine, Seoul	Academia	Big	5581	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
9	Clinicaltrials.gov	Safety and efficacy assessment of autologous bone-marrow derived adult mesenchymal stem cell therapy in patients with anoxic (or hypoxic) brain injury pilot trial	2014	Yes	Phase I/II	6 Diseases of the nervous system	Autologous	Hanyang University Seoul Hospital	Academia	Big	1862	N/R
10	Clinicaltrials.gov	A phase I/IIa, open-label, single-centre, prospective study to determine the safety and tolerability of sub-retinal transplantation of human embryonic stem cell derived retinal pigmented epithelial (MA09-hRPE) cells in patients with advanced dry age-related macular degeneration(AMD)	2012	Yes	Phase I/II	7 Diseases of the eye and adnexa	Allogeneic	CHABiotech Co.	Profit	Big	300	$ 390.144.400,00
11	Clinicaltrials.gov	Safety study of HLA -haplo matched Allogeneic bone marrow derived stem cell treatment in amyotrophic lateral sclerosis	2012	Yes	Phase I	6 Diseases of the nervous system	Allogeneic	Hanyang University Seoul Hospital (Corestem Inc. as collaborator)	Academia	Big	1862	N/R
12	Clinicaltrials.gov	Safety and tolerability of MA09-hRPE cells in patients with Stargardt's macular	2012	Yes	Phase I	7 Diseases of the eye and adnexa	Allogeneic?	CHABiotech Co.	Profit	Big	Big	$ 390.144.400,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
		dystrophy (SMD)										
13	Clinicaltrials.gov	Safety and efficacy of intracoronary adult human mesenchymal stem cells after acute myocardial infarction	2011	Yes	Phase II/III	9 Diseases of the circulatory system	Autologous	Yonsei University (FBI-Pharmicell Co. as collaborator)	Academia	Big	4983	$ 123.330.600,00
14	Clinicaltrials.gov	Safety of FURESTEM-RA Inj. in patients with moderate to severe rheumatoid arthritis (RA)	2014	Yes	Phase I	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	Kang Stem Biotech Co.	Profit	Small	1-10 employees	N/R
15	Clinicaltrials.gov	Safety and efficacy of FURESTEM-CD Inj. In patients with moderately active Crohn's disease (CD)	2013	Yes	Phase I/II	11 Diseases of the digestive system	Allogeneic	Kang Stem Biotech Co.	Profit	Small	1-10 employees	N/R
16	Clinicaltrials.gov	Safety and efficacy of FURESTEM-AD Inj. In patients with moderately subacute and chronic atopic dermatitis (AD)	2013	Yes	Phase I/II	12 Diseases of the skin and subcutaneous tissue	Allogeneic	Kang Stem Biotech Co.	Profit	Small	1-10 employees	N/R
17	Clinicaltrials.gov	Genetically modified mesenchymal stem cell theraopeutic against head and neck cancer	2014	Yes	Phase I	2 Neoplasms	N/R	Genexine Inc.	Profit	Medium	102	$ 4.103.200,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
18	Clinicaltrials.gov	Trial of autologous mesenchymal stem cells in patients with multiple system atrophy	2009	Yes	Phase II	6 Diseases of the nervous system	Autologous	Yonsei University	Academia	Big	4983	$ 123.330.600,00
19	Clinicaltrials.gov	Safety and efficacy study using gene therapy for critical limb ischemia	2010	Yes	Phase II	9 Diseases of the circulatory system	N/A	Viromed Co.	Profit	Medium	58	$ 4.793.200,00
20	Clinicaltrials.gov	Gene therapy for chronic granulomatous disease in Korea	2008	Yes	Phase I/II	3 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	N/A	Viromed Co.	Profit	Medium	58	$ 4.793.200,00
21	Clinicaltrials.gov	Efficacy and safety of TissueGene-C mixed with fibrin-glue for the patients with degenerative arthritis	2013	Yes	Phase II	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	Kolon Life Science (product of TissueGene Inc.)	Profit	Big	424	$ 114.080.000,00
22	Clinicaltrials.gov	Safety study of gene therapy for ischemic heart disease in Korea	2011	Yes	Phase I	9 Diseases of the circulatory system	N/A	Viromed Co.	Profit	Medium	58	$ 4.793.200,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
23	CRIS	A prospective, randomized multicenter, open-label, safety and preliminary efficacy study of Immunotherapy in patients with unresectable hepatocellular carcinoma (HCC) treated by transarterial chemoembolization (TACE)	2013	Yes	Phase II	2 Neoplasms	Autologous	Kyongpook National University Hospital	Academia	Big	1968	N/R
24	CRIS	Dendritic cell-based immunotherapy in patients with primary glioblastoma multiforme	2011	Yes	Phase I/II	2 Neoplasms	Autologous	Bundang CHA General Hospital (supported by CreaGene)	Non-for-profit	N/R	N/R	N/R
25	CRIS	The Safety of Human Cord Blood-derived Mesenchymal Stem Cells Therapy in Patients with Peripheral Arterial Occlusive Disease: Phase 1 Clinical Study	2010	Yes	Phase I	9 Diseases of the circulatory system	Allogeneic	Samsung Medical Centre	Non-for-profit	Big	8000	N/R
26	CRIS	Randomized exploratory clinical trial to evaluate the safety and effectiveness of cell transplantation therapy using mesenchymal stem cell in alcoholic liver cirrhosis patient	2013	Yes	Phase II	11 Diseases of the digestive system	Autologous	Yonsei University	Academia	Big	4983	$ 123.330.600,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
27	CRIS	The evaluation of effectiveness and safety for new therapy with bone marrow derived autologous mesenchymal stem cell for hepatic failure caused by alcoholic liver cirrhosis	2009	Yes	Phase II	11 Diseases of the digestive system	Autologous	Yonsei University	Academia	Big	4983	$ 123.330.600,00
28	CRIS	A Opened, Randomized, Multi-centred Phase II study on the efficacy and safety of CreaVax-HCC(Autologous Mature Dendritic Cells)in patients with hepatocellular carcinoma for comparing after a operation and/or non-operation therapy	2010	Yes	Phase II	2 Neoplasms	Autologous	Seoul National University Hospital (supported by CreaGene)	Academia	Big	5944	N/R
29	CRIS	Safety and Efficacy of Allogeneic Umbilical Cord Blood Therapy Combined With Erythropoietin in Children With Cerebral Palsy: a Double-blind, Randomized, Placebo-controlled Clinical Trial	2013	Yes	Phase II	6 Diseases of the nervous system	Allogeneic	Bundang CHA General Hospital	Non-for-profit	N/R	N/R	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
30	CRIS	A phase IIa, randomized, open-label study evaluating the safety and efficacy of CreaVax-RA combined with traditional disease modifying anti-rheumatic drugs (DMARDs) therapy in patients with moderate to severe active rheumatoid arthritis despite DMARDs therapy	2013	Yes	Phase II	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Hanyang University Seoul Hospital (sponsored by CreaGene)	Academia	Big	1862	N/R
31	CRIS	Allogeneic Umbilical Cord Blood Therapy for Children with Cerebral Palsy	2012	Yes	Phase I/II	6 Diseases of the nervous system	Allogeneic	Bundang CHA General Hospital	Non-for-profit	N/R	N/R	N/R
32	CRIS	Safety and efficacy of allogeneic umbilical cord blood therapy for children with global developmental delay	2012	Yes	Phase I/II	18 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	Allogeneic	Bundang CHA General Hospital	Non-for-profit	N/R	N/R	N/R
33	CRIS	A placebo control, double-blind, randomized, parallel-group, multi-centre Phase 3 study to determine the efficacy and safety of TissueGene-C in patients with osteoarthritis	2013	Yes	Phase III	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	Seoul National University Hospital (sponsored by Kolon Life Science)	Academia	Big	5944	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
34	CRIS	Thrombolytic efficacy of intravenous recombinant tissue plasminogen activator with different doses	2013	Yes	Phase I/II	9 Diseases of the circulatory system	N/A	Yonsei University	Academia	Big	4983	$ 123.330.600,00
35	CRIS	Phase 1/2 clinical study to evaluate safety and efficacy of allogenic adipose-derived stem cells(ALLO-ASC-TI) for the treatment of patients with lateral epicondylalgia: a randomized, placebo-controlled, double-blind, parallel-group, multi-centre study	2014	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	Seoul National University Hospital (sponsored by Anterogen)	Academia	Big	5944	N/R
36	CRIS	Intravenous Administration of Autoserum-cultured Autologous Mesenchymal Stem Cells in Ischemic Stroke: A Single Centre, Randomized, Open Label, Prospective, Phase 3 Study	2012	Yes	Phase III	9 Diseases of the circulatory system	Autologous	Samsung Medical Centre (supported by PharmiCell)	Non-for-profit	Big	8000	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
37	CRIS	A Phase I/IIa Study of CreaVax-HCC (Autologous Mature Dendritic Cells) to evaluate Safety and Efficacy in Patients with Hepatocellular carcinoma in TNM I to IIIC Stage after hepatic resection and/or other treatments (PEI, RFA, TACE)	2009	Yes	Phase I/II	2 Neoplasms	Autologous	Seoul National University Hospital (supported by CreaGene)	Academia	Big	5944	N/R
38	CRIS	Umbilical cord blood-derived mesenchymal stem cells for the treatment of steroid-refractory acute or chronic graft-versus-host-disease	2011	Yes	Phase I/II	19 Injury, poisoning and certain other consequences of external causes	Allogeneic	Samsung Medical Centre (sponsored by Medipost)	Non-for-profit	Big	8000	N/R
39	CRIS	A Phase I dose escalation clinical study to evaluate the safety and efficacy of ALLO-ASC(Allogenic adipose-derived stem cells) in the patients with Crohn's fistula.	2011	Yes	Phase I	11 Diseases of the digestive system	Allogeneic	Yonsei University (sponsored by Anterogen)	Academia	Big	4983	$ 123.330.600,00

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
40	CRIS	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Protective Efficacy and Safety of a Therapeutic Vaccine, ASP0113, in CMV-Seropositive Recipients Undergoing Allogeneic, Hematopoietic Cell Transplant(HCT)	2013	Yes	Phase III	1 Certain infectious and parasitic diseases	N/A	Asan Medical Centre (sponsored by Astellas Pharm)	Non-for-profit	Big	7529	N/R
41	CRIS	A randomized, single centre, investigator initiated clinical trial to evaluate enhancement of healing between bone tunnel and graft in anterior cruciate ligament(ACL) injury using human umbilical cord blood derived mesenchymal stem cell.	2013	Yes	Phase I/II	13 Diseases of the musculoskeletal system and connective tissue	Allogeneic	Samsung Medical Centre	Non-for-profit	Big	8000	N/R
42	CRIS	A phase I, open label, dose ranging study to evaluate the safety and tolerance of CreaVax-RA in active rheumatoid arthritis patients with usual DMARDs	2010	Yes	Phase I	13 Diseases of the musculoskeletal system and connective tissue	Autologous	Hanyang University Seoul Hospital (sponsored by CreaGene)	Academia	Big	1862	N/R

#	Source	Research project	Year	Tested in humans	Clinical trial phase	Therapeutic indication	If cell-based	Developer	Type of organisation	Size of developer	Manpower	Annual
43	ISRCTN	A phase III clinical trial for the two months safety and efficacy evaluation of Ostem™ (autologous cultured osteoblasts) in patients with fracture	2008	Yes	Phase III	19 Injury, poisoning and certain other consequences of external causes	Autologous	The Catholic University of Korea	Academia	N/R	N/R	N/R

Annex 8. Full references clinical trials

US:

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Clinical Trials:

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63. Enriched autologous fat grafting for treating pain at amputation sites, 2012 (NCT01645722).

64. Pivotal trial of Dermagraft® to treat diabetic foot ulcers, 2010 (NCT01181453).

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68. Stem cell therapy to improve burn wound healing, 2014 (NCT02104713).
69. Cell therapy for cranofacial bone defects, 2012 (NCT01616953).
70. Combination of stem cell therapy for the treatment of severe coronary ischemia, 2008 (NCT00643981).
71. Cell therapy for metastatic melanoma using CD8 enriched tumour infiltrating lymphocytes, 2010 (NCT01236573).
72. Mesenchymal stem cell therapy for lung rejection, 2014 (NCT02181712).
73. Phase II combination stem cell therapy for the treatment of severe coronary ischemia (CI), 2008 (NCT00790764).
74. Mesenchymal stem cell therapy in multiple system atrophy, 2014 (NCT02315027).
75. An investigation of the safety of 4 different doses of autologous muscle derived cells as a therapy for stress urinary incontinence, 2009 (NCT00847535).
76. Stem cell injection to treat heart damage during open heart surgery, 2012 (NCT01557543).
77. Treatment alveolar bone defects using aastrom biosciences autologous tissue repair cell therapy, 2008 (NCT00755911).
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82. An efficacy and safety study of Ixmyelocel-T in patients with critical limb ischemia (CLI), 2011 (NCT01483898).
83. Research with retinal cells derived from stem cells for myopic macular degeneration, 2014 (NCT02122159).
84. Evaluation of Prochymal® for treatment-refractory moderate-to-severe Crohn's disease, 2010 (NCT01233960).
85. Autologous muscle derived cells for female urinary sphincter repair, 2013 (NCT01893138).
86. Phase 2, randomized, double blind, placebo controlled multicenter study of autologous MSC-NTF cells in patients with ALS, 2013 (NCT02017912).
87. Adipose derived regenerative cellular therapy of chronic wounds, 2014 (NCT02092870).
88. A safety study of CNTO 2476 in patients with age-related macular degeneration, 2010 (NCT01226628).

89. Safety and effectiveness of banked cord blood or bone marrow stem cells in children with cerebral palsy (CP), 2013 (NCT01988584).
90. Bone tissue engineering using autologous bone repair cell (BRC) therapy for sinus floor bone augmentation, 2009 (NCT00980278).
91. A phase 2 trial of AMI Multistem® therapy in subjects with non-ST elevation acute myocardial infarction, 2014 (NCT02277613).
92. Laboratory-treated T cells in treating patients with high-risk relapsed acute myeloid leukemia, myelodysplastic syndrome, or chronic myelogenous leukemia previously treated with donor stem cell transplant, 2011 (NCT01640301).
93. Adipose -derived regenerative cells in total knee arthroplasty, 2014 (NCT02262988).
94. Autologous CD-19-specific T-cell infusion, 2009 (NCT00968760).
95. T-cell receptor immunotherapy targeting MAGE-A3 for patients with metastatic cancer who are HLA-A*01 positive, 2014 (NCT02153905).
96. T-cell receptor immunotherapy targeting MAGE-A3 for patients with metastatic cancer who are HLA-DP0401 positive, 2014 (NCT02111850).
97. Stem cell study for subjects with congestive heart failure, 2008 (NCT00620048).
98. Use of autologous bone marrow aspirate concentrate in painful knee osteoarthritis, 2013 (NCT01931007).
99. Laboratory-treated donor cord blood cell infusion following combination chemotherapy in treating younger patients with relapsed or refractory acute myeloid leukemia, 2012 (NCT01701323).
100. Injections of FloGraft therapy, autologous stem cells, or platelet rich plasma for the treatment of degenerative joint pain, 2013 (NCT01978639).
101. Gene therapy for fanconi anemia, 2011 (NCT01331018).
102. MSC for occlusive disease of the kidney, 2013 (NCT01840540).
103. Safety of autologous stem cell infusion for children with acquired hearing loss, 2014 (NCT02038972).
104. Immunotherapy of melanoma with tumour antigen RNA and small inhibitory RNA transfected autologous dendritic cells, 2008 (NCT00672542).
105. Evaluation of CureXcell® in treating chronic venous leg ulcers, 2014 (NCT02130310).
106. Long term follow-up study of human immunodefficiency virus type 1 (HIV-1) positive patients who have received OZ1 gene therapy as part of a clinical trial, 2010 (NCT01177059).
107. Phase I dose escalation safety study of RetinoStat in advanced age-related macular degeneration (AMD), 2011 (NCT01301443).
108. A study evaluating the safety and efficacy of the LentiGlobin BB305 drug product in severe sickle cell disease, 2014 (NCT02140554).
109. Stem cell gene for sickle cell disease, 2014 (NCT02247843).

110. Her2 chimeric antigen receptor expressing T cells in advanced sarcoma, 2009 (NCT00902044).
111. Gene therapy using anti-her-2 cells treat metastatic cancer, 2009 (NCT00924287).
112. Safety study of TissueGene-C in degenerative joint disease of the knee, 2008 (NCT00599248).
113. Transfer of genetically engineered lymphocytes in melanoma patients, 2012 (NCT01586403).
114. Redirected MazF CD4 autologous T cells for HIV gene therapy, 2013 (NCT01787994).
115. Redirected high affinity gagaspecific autologous T-cells for HIV gene therapy, 2009 (NCT00991224).
116. CT antigen TCR-redirected T-cells for ovarian cancer, 2012 (NCT01567891).
117. Anti-MART-1 F5 lymphocytes to treat high risk melanoma patients, 2008 (NCT00706992).
118. IL-12 gene and in vivo electroporation-mediated plasmid DNA vaccine therapy in patients with merkel cell cancer, 2011 (NCT01440816).
119. Tumour infiltrating lymphocytes (TIL) transduced with TGFbDNRII, 2013 (NCT01955460).
120. TGF-beta resistant cytotoxic T-lymphocytes in treatment of EBV-positive nasopharyngeal carcinoma/RESIST-NPC, 2014 (NCT02065362).
121. Activated T lymphocytes expressing CARs, relapsed CD19+ malignancies post-allo HSCT (CARPASCIO), 2014 (NCT02050347).
122. Administration of donor T-cells with the caspase-9 suicide gene, 2011 (NCT01494103).
123. Microfracture versus adipose derived stem cells for the treatment of articular cartillage defects, 2014 (NCT02090140).
124. Investigation of A-ECM for the correction of soft tissue defects, 2013 (NCT01992315).
125. Lymphodepletion plus adoptive cell transfer with high dose IL-2 in patients with metastatic melanoma, 2009 (NCT01005745).
126. Autologous dendritic cell-tumour cell imunotherapy for metastatic melanoma, 2013 (NCT01875653).
127. Allogeneic heart stem cells to achieve myocardial regeneration (ALL STAR), 2012 (NCT01458405).
128. Safety study of a dual anti-HIV gene transfer construct to treat HIV-1 infection, 2013 (NCT01734850).
129. Stem cell gene therapy for sickel cell disease, 2014 (NCT02247843).
130. A safety, tolerability, and efficacy study of VC-01 combination product in subjects with type I diabetes mellitus, 2014 (NCT02239354).
131. Safety study on GRNOPC1 in spinal cord injury, 2010 (NCT01217008).

132. Study of Gene Modified Immune Cells in Patients With Advanced Melanoma (F5), 2009 (NCT00910650).

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Clinical Trials:

12. Retinal Gene Therapy for Choroideremia Using an Adeno-associated Viral Vector (AAV2) Encoding Rab-escort Protein-1 (REP1), 2014 (N/R).
13. A study of the efficacy and safety of ABH001 in the treatment of patients with epidermolysis bullosa who have wounds that are not healing, 2012 (NCT01749306).
14. Autologous cell therapy for female stress urinary incontinence, 2009 (NCT01008943).
15. The enhanced angiogenic cell therapy- acute myocardial infarction trial (ENACT-AMI), 2009 (NCT00936819).
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17. Autologous cell therapy for treatment of fecal incontinence, 2012 (NCT01600755).
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100. Safety, efficacy and immunogenicity of autologous tumour lysate-pulsed dendritic cell therapy in patients with advanced renal cell carcinoma, 2009 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000002136).

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116. Phase I study on the combination therapy of IMF-001 and MIS416 for the treatment of patients with NY-ESO-1 expressing malignant solid tumour., 2012 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000008007).

117. Phase 1 clinical study on the combination therapy of CHP-NY-ESO-1 cancer vaccine and Poly-ICLC for the treatment of patients with NY-ESO-1 expressing refractory esophageal cancer, 2012 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000007961).

118. A randomized multicentre trial of adjuvant IMF-001 after curative resection for esophageal cancer with NY-ESO-1 antigen (phase II study), 2012 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000007905).

119. MAGE-A4 peptide vaccine study after Adoptive transfer of lymphocytes transduced with MAGE-A4-specific TCR gene, 2011 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000006507).

120. Phase I Clinical Study on the Combination Therapy of CHP-NY-ESO-1 Cancer Vaccine and MIS416 for the Treatment of Patients with NY-ESO-1 expressing Refractory Urothelial or Prostate Cancer, 2011 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000005246).

121. A clinical study of adenovirus mediated Reduced Expression in Immortalized Cells/Dickkopf-3(REIC/Dkk-3)gene therapy for prostate cancer, 2011 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000004929).

122. A clinical study of a replication-competent, recombinant herpes simplex virus type 1 (G47delta) in patients with progressive glioblastoma, 2009 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000002661).

123. Adoptive transfer of lymphocytes transduced with MAGE-A4-specific TCR gene for therapy-resistant esophageal cancer, 2009 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000002395).

124. CHP-MAGE-A4 vaccine study for MAGE-A4-expressing cancer, 2008 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000001599).

125. clinical trial of CHP-HER2 cancer vaccine with immuno-adjuvant, OK-432, for advanced breast cancer, 2008 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000001286).

126. Safety and Immunogenicity of Cholesterol-Bearing Hydrophobized Pullulan HER2 Protein 146 (CHP-HER2) and NY-ESO-1 Protein (CHP-NY-ESO-1) in Combination With OK-432 in HER2- and/or NY-ESO-1-Expressing Cancers, 2008 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000001081).

127. Adoptive transfer of autologous T cells followed by vaccination with MAGE-A4-derived peptides after chemotherapy for MAGE-A4-expressing advanced cancer patients, 2008 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000001063).

128. Long-term follow-up clinical study of cultured epithelial autografts (CEA, J-TEC-01) for patients with giant congenital melanocytic nevi., 2014 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000013361).

129. A clinical study of alveolar bone tissue engineering using autologous bone marrow stromal cells, 2011 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000006255).

130. Clinical trial on in situ bone tissue engineering using bioactive bone substitute for acceleration of bone regeneration in sinus floor augmentation, 2011 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000005919).

131. Development of implant-type tissue-engineered cartilage for patients with nasal deformity in cleft lip and palate - implant-type tissue-engineered cartilage, which is made by applying autologous auricular chondrocytes to scaffolds consisting of atelocollagen hydrogel and poly-L-lactic acid (PLLA) porous body, 2011 (http://rctportal.niph.go.jp/en/detail?trial_id=UMIN000005472).

Korea:

1. Jo, D. I., Yang, H. J., Kim, S. H., et al. Coverage of skin defects without skin grafts using adipose-derived stem cells. Aesthetic Plast Surg. 2013 Oct;37(5):1041-51.
2. Kang, H. J., Kim, M. K., Lee, H. Y., et al. Five-year results of intracoronary infusion of the mobilized peripheral blood stem cells by granulocyte colony-stimulating factor in patients with myocardial infarction. Eur Heart J. 2012 Dec;33(24):3062-9.
3. Koh, Y. G., Choi, Y. J. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. Knee. 2012 Dec;19(6):902-7.
4. Lee, J., Sung, H. M., Jang, J. D., Park, Y. W., Min, S. K. and Kim, E. C. Successful reconstruction of 15-cm segmental defects by bone marrow stem cells and resected autogenous bone graft in central hemangioma. J Oral Maxillofac Surg. 2010 Jan;68(1):188-94.
5. Lee, P. H., Kim, J. W., Bang, O. Y., Ahn, Y. H., Joo, I. S. and Huh, K. Autologous mesenchymal stem cell therapy delays the progression of neurological deficits in patients with multiple system atrophy. Clin Pharmacol Ther. 2008 May;83(5):723-30.
6. Lee WY, Park KJ, Cho YB, Yoon SN, Song KH, Kim do S, Jung SH, Kim M, Yoo HW, Kim I, Ha H, Yu CS. Autologous adipose tissue-derived stem cells treatment demonstrated favourable and sustainable therapeutic effect for Crohn's fistula. Stem Cells. 2013 Nov;31(11):2575-81.
7. Cho YB, Lee WY, Park KJ, Kim M, Yoo HW, Yu CS. Autologous adipose tissue-derived stem cells for the treatment of Crohn's fistula: A Phase I clinical study. Cell Transplant. 2013;22(2):279-85.
8. Kim M, Kim I, Lee SK, Bang SI, Lim SY. Clinical trial of autologous differentiated adipocytes from stem cells derived from human adipose tissue. Dermatol Surg. 2011 Jun;37(6):750-9.

Clinical Trials:

9. Safety and efficacy assessment of autologous bone-marrow derived adult mesenchymal stem cell therapy in patients with anoxic (or hypoxic) brain injury pilot trial, 2014 (NCT02210624).
10. A phase I/IIa, open-label, single-centre, prospective study to determine the safety and tolerability of sub-retinal transplantation of human embryonic stem cell derived retinal pigmented epithelial (MA09-hRPE) cells in patients with advanced dry age-related macular degeneration(AMD), 2012 (NCT01674829).
11. Safety study of HLA -haplo matched Allogeneic bone marrow derived stem cell treatment in amyotrophic lateral sclerosis, 2012 (N/R).
12. Safety and tolerability of MA09-hRPE cells in patients with Stargardt's macular dystrophy (SMD), 2012 (NCT01625559).
13. Safety and efficacy of intracoronary adult human mesenchymal stem cells after acute myocardial infarction, 2011 (NCT01392105).
14. Safety of FURESTEM-RA Inj. in patients with moderate to severe rheumatoid arthritis (RA), 2014 (NCT02221258).

15. Safety and efficacy of FURESTEM-CD Inj. In patients with moderately active Crohn's disease (CD), 2013 (NCT02000362).

16. Safety and efficacy of FURESTEM-AD Inj. In patients with moderately subacute and chronic atopic dermatitis (AD), 2013 (NCT01927705).

17. Genetically modified mesenchymal stem cell theraopeutic against head and neck cancer, 2014 (NCT02079324).

18. Trial of autologous mesenchymal stem cells in patients with multiple system atrophy, 2009 (NCT00911365).

19. Safety and efficacy study using gene therapy for critical limb ischemia, 2010 (NCT01064440).

20. Gene therapy for chronic granulomatous disease in Korea, 2008 (NCT00778882).

21. Efficacy and safety of TissueGene-C mixed with fibrin-glue for the patients with degenerative arthritis, 2013 (NCT01825811).

22. Safety study of gene therapy for ischemic heart disease in Korea, 2011 (NCT01422772).

23. A prospective, randomized multicentre, open-label, safety and preliminary efficacy study of Immunotherapy in patients with unrespectable hepatocellular carcinoma (HCC) treated by transarterial chemoembolization (TACE), 2013 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=3741).

24. Dendritic cell-based immunotherapy in patients with primary glioblastoma multiforme, 2011 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=4038).

25. The Safety of Human Cord Blood-derived Mesenchymal Stem Cells Therapy in Patients with Peripheral Arterial Occlusive Disease: Phase 1 Clinical Study, 2010 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=1423).

26. Randomized exploratory clinical trial to evaluate the safety and effectiveness of cell transplantation therapy using mesenchymal stem cell in alcoholic liver cirrhosis patient, 2013 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=2638).

27. The evaluation of effectiveness and safety for new therapy with bone marrow derived autologous mesenchymal stem cell for hepatic failure caused by alcoholic liver cirrhosis, 2009 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=1625).

28. A Opened, Randomized, Multi-centred Phase II study on the efficacy and safety of CreaVax-HCC(Autologous Mature Dendritic Cells)in patients with hepatocellular carcinoma for comparing after a operation and/or non-operation therapy, 2010 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=3770).

29. Safety and Efficacy of Allogeneic Umbilical Cord Blood Therapy Combined With Erythropoietin in Children With Cerebral Palsy: a Double-blind, Randomized, Placebo-controlled Clinical Trial, 2013 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=3574).

30. A phase IIa, randomized, open-label study evaluating the safety and efficacy of CreaVax-RA combined with traditional disease modifying anti-rheumatic drugs

(DMARDs) therapy in patients with moderate to severe active rheumatoid arthritis despite DMARDs therapy, 2013 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=3319).

31. Allogeneic Umbilical Cord Blood Therapy for Children with Cerebral Palsy, 2012 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=2264).
32. Safety and efficacy of allogeneic umbilical cord blood therapy for children with global developmental delay, 2012 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=2263).
33. A placebo control, double-blind, randomized, parallel-group, multi-centre Phase 3 study to determine the efficacy and safety of TissueGene-C in patients with osteoarthritis, 2013 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=4366).
34. Thrombolytic efficacy of intravenous recombinant tissue plasminogen activator with different doses, 2013 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=3560).
35. Phase 1/2 clinical study to evaluate safety and efficacy of allogenic adipose-derived stem cells(ALLO-ASC-TI) for the treatment of patients with lateral epicondylalgia: a randomized, placebo-controlled, double-blind, parallel-group, multi-centre study, 2014 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=3914).
36. Intravenous Administration of Autoserum-cultured Autologous Mesenchymal Stem Cells in Ischemic Stroke: A Single Centre, Randomized, Open Label, Prospective, Phase 3 Study, 2012 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=2567).
37. A Phase I/IIa Study of CreaVax-HCC (Autologous Mature Dendritic Cells) to evaluate Safety and Efficacy in Patients with Hepatocellular carcinoma in TNM I to IIIC Stage after hepatic resection and/or other treatments (PEI, RFA, TACE), 2009 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=3150).
38. Umbilical cord blood-derived mesenchymal stem cells for the treatment of steroid-refractory acute or chronic graft-versus-host-disease, 2011 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=1838).
39. A Phase I dose escalation clinical study to evaluate the safety and efficacy of ALLO-ASC(Allogenic adipose-derived stem cells) in the patients with Crohn's fistula., 2011 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=1436).
40. A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Protective Efficacy and Safety of a Therapeutic Vaccine, ASP0113, in CMV-Seropositive Recipients Undergoing Allogeneic, Hematopoietic Cell Transplant(HCT), 2013 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=4398).
41. A randomized, single centre, investigator initiated clinical trial to evaluate enhancement of healing between bone tunnel and graft in anterior cruciate ligament(ACL) injury using human umbilical cord blood derived mesenchymal stem cell., 2013 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=4724).

42. A phase I, open label, dose ranging study to evaluate the safety and tolerance of CreaVax-RA in active rheumatoid arthritis patients with usual DMARDs, 2010 (https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=1645).

43. A phase III clinical trial for the two months safety and efficacy evaluation of Ostem™ (autologous cultured osteoblasts) in patients with fracture, 2008 (http://www.isrctn.com/ISRCTN10637905?q=celltherapy&filters=recruitmentCountry:Korea\South&sort=&offset=5&totalResults=5&page=1&pageSize=10&searchType=advanced-search).

Annex 9. Full search strategy related to the analysis of the economic aspects of the advanced therapies market

Search date: 18-11-2015

Attention: all components (3 or 4) are combined with “AND”

Search strategy intellectual property legislation

ATMP

atmp[tiab] or advanced therap*[tiab] or advanced therapy medicinal product*[tiab] or regenerative medicine[tiab] or cell therap*[tiab] or cell-based product*[tiab] or cell-based therap*[tiab] or gene therap*[tiab] or tissue engineering[tiab] or tissue engineered product*[tiab] or cell- and tissue-based therapy[mesh] or tissue engineering[mesh] or regenerative medicine[mesh] or genetic therapy[mesh]

IPR

(intellectual[tiab] and propert*[tiab]) or patent*[tiab] licens*[tiab] or IPR[tiab] or (protect*[tiab] and (product*[tiab] or invest*[tiab] or therap*[tiab] or develop*[tiab])) or Intellectual Property[Mesh] or (patent*[tiab] and (jurisprudenc*[tiab] or Jurisprudence[Mesh])) or (intellectual[tiab] and propert*[tiab] and (jurisprudenc*[tiab] or jurisprudence[Mesh]))

Country filters:

- united states[mesh] or usa[ad] or usa[tiab] or us[tiab];
- canada[mesh] or canada[ad] or canada[tiab];
- japan[mesh] or japan[ad] or japan[tiab] or jpn[tiab] or jp[tiab];
- republic of korea[mesh] or republic of korea[ad] or south korea[ad] or republic of korea[tiab] or south korea[tiab] or kor[tiab] or kr[tiab].

Number of hits

US: 1710 (4 inclusions)
CA: 224 (1 inclusion)
JP: 282 (2 inclusions)
SK: 60 (0 inclusions)

Search strategy overview incentives

Regulation / development

regulat*[tiab] or polic*[tiab] or legal framework[tiab] or legislation[tiab] or law[tiab] or requirement*[tiab] or licenc*[tiab] or approval[tiab] or marketing[tiab] or commerciali*[tiab] or develop*[tiab] or invest*[tiab] or policy[mesh] or government regulation[mesh] or legislation as topic[mesh] or marketing[mesh] or drug approval[mesh] or investments[mesh] or commerce[mesh]

ATMP

atmp[tiab] or advanced therap*[tiab] or advanced therapy medicinal product*[tiab] or regenerative medicine[tiab] or cell therap*[tiab] or cell-based product*[tiab] or cell-based therap*[tiab] or gene therap*[tiab] or tissue engineering[tiab] or tissue engineered product*[tiab] or cell- and tissue-based therapy[mesh] or tissue engineering[mesh] or regenerative medicine[mesh] or genetic therapy[mesh]
Incentives

incentive*[tiab] or encourage*[tiab] or support*[tiab] or deferral*[tiab] or referral*[tiab] or waiver*[tiab] or advice*[tiab] or advising[tiab] or reward*[tiab] or award*[tiab] or facilit*[tiab] or fund*[tiab] or network*[tiab] or exclusivit*[tiab] or conditional[tiab] or exceptional[tiab] or exemption*[tiab] or instrument*[tiab] accelerat*[tiab] or attract*[tiab]

Country filters:

- united states[mesh] or usa[ad] or usa[tiab] or us[tiab];
- canada[mesh] or canada[ad] or canada[tiab];
- japan[mesh] or japan[ad] or japan[tiab] or jpn[tiab] or jp[tiab];
- republic of korea[mesh] or republic of korea[ad] or south korea[ad] or republic of korea[tiab] or south korea[tiab] or kor[tiab] or kr[tiab].

Number of hits

US: 848 (5 inclusions)
CA: 94 (6 inclusions)
JP: 225 (1 inclusion)
SK: 60 (0 inclusions)

Search strategy time to approval/commercialisation

ATMP

atmp[tiab] or advanced therap*[tiab] or advanced therapy medicinal product*[tiab] or regenerative medicine[tiab] or cell therap*[tiab] or cell-based product*[tiab] or cell-based therap*[tiab] or gene therap*[tiab] or tissue engineering[tiab] or tissue engineered product*[tiab] or (substantial*[tiab] and manipulate*[tiab]) or cell- and tissue-based therapy[mesh] or tissue engineering[mesh] or regenerative medicine[mesh] or genetic therapy[mesh]

Procedure time

((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and approval[tiab]) or
((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and (procedur*[tiab]) or
((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and (phase[tiab])) or
((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and commerciali*[tiab]) or
((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and marketing[tiab]) or
((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and "Commerce"[Mesh]) or
((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and (post[tiab] and approval[tiab])) or
((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and (authorisation[tiab] or authorisation[tiab])) or
((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and pricing[tiab]) or
((time[tiab] or duration[tiab] or period[tiab] or length[tiab]) and reimbursement[tiab]) or

filter US: Hemacord*[tiab] or TheraCys[tiab] / filter Canada: Prochymal [tiab] / filter Japan: JACC [tiab] / filter South Korea:

Country filters:

- united states[mesh] or usa[ad] or usa[tiab] or us[tiab] or Hemacord*[tiab] or TheraCys[tiab];
- canada[mesh] or canada[ad] or canada[tiab] or Prochymal[tiab];
- japan[mesh] or japan[ad] or japan[tiab] or jpn[tiab] or jp[tiab] or JACC[tiab];
- republic of korea[mesh] or republic of korea[ad] or south korea[ad] or republic of korea[tiab] or south korea[tiab] or kor[tiab] or kr[tiab] or Cupistem [tiab] or Kaloderm [tiab].

Number of hits

US: 757 (13 inclusions)
CA: 78 (1 inclusion)
JP: 137 (4 inclusions)
SK: 28 (0 inclusions)

*Hemacord was replaced by Provenge as Hemacord does not to meet the definition of advanced therapies as used in the report.

Pricing and Reimbursement

The search string:

<Country> AND healthcare system OR health system AND coverage OR pricing OR reimbursement was entered in the databases of EMBASE, Web of Science, EconLit and Pubmed.

Several adjustments were made in the different filters and search fields of the specific database.

EMBASE

The string was adjusted by specifying the filers to([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND ([article]/lim OR [review]/lim OR [short survey]/lim) AND [english]/lim AND [embase]/lim AND advanced AND ('therapy'/exp OR therapy).

Web of Science

The Web of Science advanced search could be specified by using term such as “title” and “Topic” before the keywords of the search string. For each of the jurisdictions studied in the study, the country name was used as a filter, the language of the articles was set to English, document types were set to article or review and depending on the number of hits, the publication years were adjusted.

Depending on the topics of the papers, filters were adjusted to match health related articles, such as: primary health care, health policy services, emergency medicine, health care sciences.

EconLit

The advanced search in EconLit was determined by adding he term “TI” (Title/Abstract) in front of every word of the search string. Due to subscription limitations, these were the only adjustments that could be made in EconLit.

Pubmed

Pubmed’s advanced search provided the possibility to insert the term “[Title/Abstract] in front of the search terms.

Annex 10. Status of Selected IP Legislation in the US (The 114th Congress)

Table A10.1 Status of selected IP Legislation in the US

Bill Number	Title	Sponsor	Summary	Major Activity	Date introduced
H.R. 95	Recognizing the importance of transformative breakthroughs in biomedicine, biotechnology, and life sciences in the diagnosis, management, curing, and treatment of illness and the existence...	Rep. Vargas, Juan [D-CA-51]	A resolution, not a bill.		02/05/2015
S. 2019	Preserve Access to Affordable Generics Act	Klobuchar (D-MN) & Grassley (R-IA)	To prohibit brand name drug companies from compensating generic drug companies to delay the entry of a generic drug into the market.	Introduced and referred to the Senate Judiciary Committee (9/9/15)	9-9-15
S. 2041	Promoting Life-Saving Therapies for Neonates Act	Casey (D-PA) & Menéndez (D, NJ) & others	To promote the development of neonatal drugs.	Introduced and referred to the Committee on Health, Education, Labour, and Pensions (9/16/2015)	9-16-15
S. 1890	Trade Secrets Act of 2015 House companion H.R. 3326	Hatch (R-UT) & Coons (D-DE); original cosponsors Baldwin, Durbin, Flake, Tillis	Would modify chapter 90 of title 18, USC, to provide Federal jurisdiction for theft of trade secrets	Introduced and referred to the Senate Judiciary Committee (7/29/15)	7-29-15
H.R. 3326	Trade Secrets Act of 2015 Senate companion S. 1890	Collins (R-GA-9) Nadler (D-NY-10) & 14 original cosponsors	Would modify chapter 90 of title 18, USC, to provide Federal jurisdiction for theft of trade secrets.	12/02/2015 Committee on the Judiciary. Hearings held.	7-29-15

Bill Number	Title	Sponsor	Summary	Major Activity	Date introduced
Draft bill	Innovation Promotion Act	Boustany (R-LA-3) & Neal (D-MI-1)	Would amend tax code deduction for "innovation box" profit from the use of U.S. innovations IP by establishing a 10% tax rate on profits.	Draft circulated	Draft circulated 7-29-15
S. 1402	Patents for Humanity Program Improvement Act	Leahy (D-VT) & Grassley (R-IA)	Would allow acceleration certificates awarded under the Patents for Humanity Program to be transferrable.	Introduced and referred to the Senate Judiciary Committee (5/20/15)	5-20-15
S. 1137	Protecting American Talent and Entrepreneurship Act (PATENT) Act	Grassley (R-IA); original cosponsors Leahy, Cornyn, Schumer, Hatch, Klobuchar, Lee	Would strengthen patent system while ensuring the system works effectively to address abusive practices and inefficiencies.	Introduced and referred to the Senate Judiciary Committee (4/29/15); Committee hearing (5/7/15); Committee approved 16-4 (6/4/15); 09/08/2015 Placed on Senate Legislative Calendar under General Orders. Calendar No. 203	4-29-15
H.R. 2045	Targeting Rogue and Opaque Letters Act (TROL)	Burgess (R-TX-26); original cosponsors Harper, Kaptur, Kinzinger, Lance, Mullin	Intended to address the problem of abusive patent demand letters.	Energy and Commerce Subcommittee hearing (4/16/15); Reported out of Subcommittee (4/22/15); Introduced and referred to the Energy & Commerce Committee (4/28/15); Reported out of Committee 30-22 (4/29/15) 05/01/2015 Referred to the Subcommittee on Commerce, Manufacturing, and Trade	4-28-15

Bill Number	Title	Sponsor	Summary	Major Activity	Date introduced
H.R. 1896	Demand Letter Transparency Act	Polis (D-CO-2), Deutch (D-FL-21), & Marino (R-PA-10)	Intended to make patent demand letters more detailed, and ramp up oversight & enforcement.	Introduced and referred to the House Judiciary Committee (4/20/15) 05/15/2015 Referred to the Subcommittee on Courts, Intellectual Property, and the Internet	4-20-15
H.R. 1791	Grace Period Restoration Act Senate companion bill S. 926	Sensenbrenner (R-WI 5) & Conyers (D-MI-13)	Would restore the effective one-year "grace period" for inventors who publicly disclose discoveries prior to filing a patent application on those discoveries.	Introduced and referred to the House Judiciary Committee (4/14/15), 05/15/2015 Referred to the Subcommittee on Courts, Intellectual Property, and the Internet.	4-14-15
S. 926	Grace Period Restoration Act House companion bill H.R. 1791	Baldwin (D-WI) & Vitter (R-LA)	Would restore the effective one-year "grace period" for inventors who publicly disclose discoveries prior to filing a patent application on those discoveries.	Introduced and referred to the Senate Judiciary Committee (4/14/15) 05/15/2015 Referred to the Subcommittee on Courts, Intellectual Property, and the Internet.	4-14-15
S. 632	Support Technology & Research for Our Nation's Growth (STRONG) Patents Act	Coons (D-DE), Durbin (D-IL), & Hirono (D-HI)	Would address abusive patent litigation, allow FTC to crack down on abusive demand letters, and ensure USPTO has resources needed.	Introduced and referred to the Senate Judiciary Committee (3/3/15); Senate Judiciary hearing (3/18/15); Senate Small Business hearing (3/19/15)	3-3-15
H.R. 9	The Innovation Act	Goodlatte (R-VA-6)	A bill targeting abusive patent litigation making corrections and improvements to the 2011	Introduced and referred to the House Judiciary Committee (2/5/15); Subcommittee	2-5-15

Bill Number	Title	Sponsor	Summary	Major Activity	Date introduced
			Leahy-Smith America Invents Act.	hearings held (3/25/15) & (4/14/15); Marked up favourably by Committee 24-8 (6/11/15)	
H.R. 236	Foreign Counterfeit Prevention Act	Poe (R-TX-2); original cosponsors Chabot, Farenthold, Lofgren	Allows CBP to share unredacted info on suspect counterfeit/pirated goods w/ IP owners to verify goods, to prevent counterfeit/pirated goods from entering the US.	Introduced and referred to the House Judiciary Committee (1/9/15)	1-9-15
H.R. 639	Improving Regulatory Transparency for New Medical Therapies Act	Rep. Pitts, Joseph R. [R-PA-16]	Amends the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to delay the effective date of approval of a drug, biological product, or animal drug for which the Food and Drug Administration (FDA) recommends controls under the Controlled Substances Act until the Department of Justice (DOJ) issues a final interim rule for the drug.	11/25/2015 Became Public Law No: 114-89.	2-2-15
S. 2030	Advancing Targeted Therapies for Rare Diseases Act of 2015	Sen. Bennet, Michael F. [D-CO]	To allow the sponsor of an application for the approval of a targeted drug to rely upon data and information with respect to such sponsor's previously approved targeted drugs.	09/15/2015 Read twice and referred to the Committee on Health, Education, Labour, and Pensions	9-15-15

Bill Number	Title	Sponsor	Summary	Major Activity	Date introduced
H.R. 3731	RaD Fund Act	Rep. Vargas, Juan [D-CA-51]	To establish a Rare Disease Therapeutics Corporation to encourage the development of high-risk, high-return therapies for rare diseases, and for other purposes.	10/16/2015 Referred to the Subcommittee on Health.	10/9/15
H.R. 2629	Antibiotic Development to Advance Patient Treatment Act	Rep. Shimkus, John [R-IL-15]	To amend the Federal Food, Drug, and Cosmetic Act with respect to the approval of certain antibacterial and antifungal drugs, and for other purposes.	06/05/2015 Referred to the Subcommittee on Health.	6/3/15
H.R. 6	21st Century Cures Act	Rep. Upton, Fred [R-MI-6]	Includes (Sec. 1002) to establish a NIH Innovation Fund is established to fund the development and implementation of a strategic plan, early stage investigators, and high-risk, high-reward research.	07/13/2015 Received in the Senate and Read twice and referred to the Committee on Health, Education, Labour, and Pensions.	5/19/15
S. 2067	EUREKA Act	Sen. Wicker, Roger F. [R-MS]	To establish EUREKA Prize Competitions to accelerate discovery and development of disease-modifying, preventive, or curative treatments for Alzheimer's disease and related dementia, to encourage efforts to enhance detection and diagnosis of such diseases, or	09/22/2015 Read twice and referred to the Committee on Health, Education, Labour, and Pensions.	9/22/16

Bill Number	Title	Sponsor	Summary	Major Activity	Date introduced
			to enhance the quality and efficiency of care of individuals with such diseases.		
H.R. 971	Orphan Product Extensions Now Accelerating Cures and Treatments Act of 2015	Sen. Hatch, Orrin G. [R-UT]	Amends the Federal Food, Drug, and Cosmetic Act to require the Department of Health and Human Services (HHS) to extend by six months the exclusivity period for a drug or biological product approved by the Food and Drug Administration (FDA) when the product is additionally approved to prevent, diagnose, or treat a new indication that is a rare disease or condition (also known as an “orphan disease”).	5/21/2015 Read twice and referred to the Committee on Health, Education, Labour, and Pensions.	5/21/15
H.R. 45	Triple-Negative Breast Cancer Research and Education Act of 2015	Rep. Jackson Lee, Sheila [D-TX-18]	To provide for research and education with respect to triple-negative breast cancer, and for other purposes.	01/09/2015 Referred to the Subcommittee on Health.	1/6/15