Toward expanded patient access to gene and cell therapy products: a comparative study of the regulatory approaches in the European Union, the United States and Japan

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Dr. Valeria Facchinetti

aus Trescore Balneario (Italien)

Bonn 2017

Betreuer und 1. Referent: Frau Prof. Dr. Christa Schröder

Zweiter Referent: Frau Dr. Bettina Fiedler

Table of Contents

List of abbreviations

AHC	APEC Harmonisation Centre
APEC	Asia-Pacific Economic Cooperation
ARM	Alliance for Regenerative Medicine, USA
ASEAN	Association of Southeast Asian Nations
ASRM	Act on the Safety of Regenerative Medicine
ATIMP	Investigational ATMP
ATMP	Advanced Therapy Medicinal Products
BLA	Biologics License Application
BWP	Biologics Working Party
CAT	Committee for Advanced Therapies
CBER	Center for Biologics Evaluation and Research
CC	Confidentiality Commitment
CDER	Center for Drug Evaluation and Research
CDRH	Center for Device and Radiological Health
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CHMP	Committee for Human Medicinal Products
CMC	Chemistry, Manufacturing, and Controls
CO	Cabinet Ordinance
CPWP	Cell-based Product Working Party
CT	Clinical Trial
CTA	Clinical Trial Authorisation
CTFG	Clinical Trial Facilitation group
CTMP	Cell Therapy Medicinal Product
CTN	Clinical Trial Notification
EC	European Commission
EDQM	European Directorate for the Quality of Medicines and HealthCare
ELD	Evaluation and Licensing Division
EMA	European Medicine Agency
EU	European Union
EWP	Efficacy Working Party
FD&C Act	Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration

FIH	First-in-human
FIRM	Forum for Innovative Regenerative Medicine
GCP	Good Clinical practice
GCT	Gene and Cell Therapy
GLP	Good Laboratory Practice
GMO	Genetically modified organism
GT	Gene therapy
GTMP	Gene Therapy Medicinal Product
GTWP	Gene Therapy Working Party
GVP	Good Vigilance Practice
HCT/P	Human cell tissue and cellular and tissue-based product
HE	Hospital Exemption
HMA	Heads of Medicines Agencies
HSA	Health Science Authority, Singapore
HSC	Health Science Council
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IPRF	International Pharmaceutical Regulators Forum
iPS	Induced pluripotent stem cells
IRB	Institutional Review Board
IRPF	International Pharmaceutical Regulators Forum
J-GCP	Japanese good clinical practice
JPMA	Japanese Pharmaceutical Manufacturers Association
JSRM	Japanese Society for Regenerative Medicine
LSIF	Life Science Innovation Forum
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MCP	Minimum Consensus Package

MHLW	Ministry of Health, Labour and Wealth
MN	MHLW Ministerial Notification
MO	MHLW Ministerial Ordinance
MOA	Mechanism of Action
MOU	Memorandum of Understanding
MRED	Medical Device and Regenerative Medicine Product Evaluation Division
MS	Member State
NCA	National Competent Authority
NDA	New Drug Application
NIBIOHN	National Institutes of Biomedical Innovation, Health and Nutrition
NIH	National Institutes of Health
NIHS	National Institute of Health Science
OCP	Office of Combination Products
OCTP	Office of Cellular and Tissue-based Products
PAHO	Pan American Health Organisation
PAL	Pharmaceutical Affairs Law
Ph. Eur.	European Pharmacopoeia
PHS Act	Public Health Service Act
PhWP	Pharmacovigilance Working Party
PMC	Post-marketing commitments
PMD Act	Pharmaceuticals and Medical Devices Act (revised PAL)
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	Post-marketing requirement
POC	Proof of concept
PPHS	Patient Proposed Health Service
PREA	Paediatric Research Equity Act
PSA	Parallel Scientific Advice
RFD	Request for Designation
RHSC	Regulatory Harmonisation Steering Committee
SME	Small and Medium Sized Enterprise
SPA	Special Protocol Assessment
SWP	Safety Working Party
TEP	Tissue Engineered Products
TTP	Target Product Profile

US	United States
VHP	Voluntary Harmonisation Procedure
WHO	World Health Organisation
WP	Working Party

1. Introduction

Gene and cell therapy (GCT) products constitute a class of heterogeneous biopharmaceuticals with the potential to provide innovative treatment approaches for a broad range of medical conditions for which conventional approaches have been proved inadequate. The field of gene and cellular therapies is rapidly expanding, as demonstrated by the number of ongoing clinical trials and research activities [1-5], suggesting a large pipeline of therapies under development. Despite their clear potential, only a few GCT have reached the market so far, resulting in a very limited impact on patients and society.

In the EU, for instance, nine years after the Regulation on the Advanced Therapy Medicinal Products (ATMP) came into force, only 8 ATMPs have received EU-wide marketing authorisation, 3 of which have been suspended or withdrawn because commercially unsuccessful. The number of authorized GCT products is not higher in other jurisdictions, with a few exceptions such as South Korea, where as of December 2014, 18 advanced therapies had been approved [4].

Because of their scientific and technical complexity, these products pose unique regulatory challenges. Different types of regulatory frameworks and national/regional requirements have been developed or are under development to confront these challenges. Efforts have been made in many jurisdictions to reach a balance between promotion of practical applications of these innovative therapies and regulatory requirements safeguarding public health. However, being these therapies at the foreground of technical and scientific innovation, a continuous reshaping of the regulatory framework is required to respond to the progression of scientific knowledge and establishment of new standards and methods.

The scope of this thesis is the analysis of the regulatory frameworks currently in force for gene and cell based therapies in the three ICH Jurisdictions: the European Union (EU), the United States (US), and Japan. As the detailed analysis of the European framework has been subject of previously submitted MDRA master thesis, only an overview is provided here, highlighting the aspects more relevant for the comparison, whereas the regulatory frameworks of the US and Japan are described in greater detail. Key aspects of this analysis include: regulatory pathways for clinical trials and marketing authorisation; quality and manufacturing requirements; and post-marketing requirements adopted by the different jurisdictions to address the challenges posed by this category of medicinal products. Particular emphasis has been given to the mechanisms to expedite the approval process with the aim to ensure early patients' access and to the alternative pathways in place in each jurisdiction allowing access to these therapies outside of clinical trials and marketed products. In addition, in the view of the global development of these products, this study includes an overview of ongoing international initiatives to leverage the regulatory

efforts and achieve regulatory harmonisation/convergence to facilitate global availability of safe and effective advanced therapies in a timely manner.

For the purpose of this study, the terms “gene and cell therapies (GCT)” and “advanced therapies” are used indistinctly referring to innovative biological products for human use based on genes, cells and tissues. A more specific terminology is used in the context of each specific jurisdiction.

1.1. Challenges in the development and commercialisation of gene and cell based medicinal products

The biological and technological complexity and high heterogeneity of GCTs pose scientific and regulatory challenges not seen for other medicinal products, impacting the entire development process and affecting these products even after market access.

Challenges in safety, quality and characterisation. More than for other medicinal products, the quality of gene and cell-based products have a direct impact on safety and efficacy, as a not adequately defined quality profile may jeopardize the results of pre-clinical and clinical studies. Manufacturing involves the use of complex starting material, including cells, tissue, or vectors, and requires reagents and excipients of biological origin for which specific quality requirements need to be met to ensure consistent biological activity across lots. Moreover, the issue of transmission of adventitious agents (e.g. growth factors, antibodies and enzymes) must be comprehensively addressed. Microbiological control and testing for adventitious agents can be very challenging since it is strictly dependent on the product characteristics. Specific standards for manufacturing and quality testing methods as well as reference materials are often not available and must be established during the product development for each specific product [6]. Additional manufacturing constraints apply to cell-based therapies, including tissue-engineered products and genetically modified cells, which are extremely sensitive to the manufacturing environment. Limited production scale and short shelf-life before administration or cryopreservation pose additional challenges to quality controls and release testing. Heterogeneity of starting material and donor variability impact the setting of the appropriate specifications. Potency, namely a quantitative measure of biological activity using a relevant assay based on the mode of action (MOA), is a critical quality attribute for biological products, as it contributes to assure identity, purity and stability as well as to assess comparability. However, the MOA may be multifactorial or not fully characterized for many GCT products, and selection and development of potency assays capable to detect changes in their quality and activity is particularly demanding. In addition, for certain therapies, acquisition of the MOA occurs after maturation *in vivo* or migration to distal sites adding an additional layer of complexity to the required potency testing [7-9].

Pre-clinical development challenges. Standardized approaches to preclinical testing are usually not applicable to GCT products due to their heterogeneity and biological complexity. The selection of appropriate animal models for the proof of concept (POC) and pre-clinical safety assessment studies are the most critical steps. Animal models of human diseases may be missing, may not be predictive of human effects or may lack the basic characteristics necessary for testing potential therapeutic effects. Complex testing strategies can be established for the evaluation of the therapeutic effects (e.g. use of knock out animals to mimic the human disease or of tumour bearing immune-deficient animals reconstituted with a human immune system), but usually don't allow safety assessment [7, 8, 10].

Clinical development challenges. Demonstration of efficacy is the major challenge in the field of GCT products and submission of insufficient efficacy data is the principal reason for failure to obtain a marketing authorisation [7]. GCT products are often developed for rare or orphan diseases or to address unmet medical needs: lack of knowledge of disease mechanisms, limited number of patients available, statistical difficulties due to small patient population, unavailability of comparators, are all factors impacting clinical trial design and outcome. Additionally, lack of knowledge of previous exposure to humans and difficulty in the determination of dose and regimen pose further challenges. Certain GCT products are administrated with potentially invasive methods (e.g. via catheters or specific devices for intracranial, intramyocardial delivery, or other surgical procedures), which can prevent placebo controlled clinical trial designs. In addition, clinical endpoints as primary clinical outcome measures are often not suitable for advanced therapy and different clinical outcome measures must be developed to indicate efficacy for advanced therapies [7, 8].

Manufacturing and distribution challenges. Whereas manufacturing processes of GT products are similar to those of many biopharmaceuticals, are controllable, and do not present particular issues in scalability, storage, and transportation, manufacturing and clinical delivery of cell-based therapies presents a set of unique challenges which are partially dependent of whether the product is allogeneic or autologous [7]. The 'one-size-fits-all' approach cannot be applied to cell therapy products and alternative product specific manufacturing and distribution approaches must be developed. One of the mayor issues is the development of suitable scalable manufacturing processes capable to produce a clinically meaningful cell number without negatively impacting the quality and the therapeutic potential of the cells [3]. The clinical delivery of cell-based products is complicated in the autologous setting by the need to scale-out rather than scale-up production and a complex supply logistic due to the short shelf-live and sensitivity to shipping conditions of these products (e.g. Provenge has a shelf life of 18 h at 2-8 °C and must be infused within 3 hours once opened [11] and Strimvelis has a shelf life of 6 hours at 15-30 °C [12, 13]). Alternative approaches (centralized vs distributed models) must therefore be

employed, depending on the indication and prevalence of the disease and the method of preservation of the product. The centralized approach is based on a central processing facility (with integrated biobank and cryopreservation protocols) serving several specialized clinical centres to which the patients need to travel for treatment. This approach has been used by Tigenix for ChondroCelect [14] and will be used by GlaxoSmithKline for Strimvelis, the first *ex vivo* gene therapy product approved in EU, which will be administered to patients in Milan, where is manufactured [13]. The decentralized approach consists in scaling out production to multiple manufacturing sites or directly at bedside within hospital settings by means of a closed, automated processing system [15]. The requirements for regulatory approval, GMP compliance and level of validation are strictly dependent on the manufacturing and distribution approaches [16].

Specific safety issues. Specific sets of safety concerns are associated to GCT products, such as the risk of integrational mutagenesis for GT products, potential prolonged biological activity after a single administration, immunogenicity, bio-distribution issues and unintended effects, ectopic tissue formation, for cell-based products [7, 8].

Securing product reimbursement. A marketing authorisation granted by the competent regulatory agency is a *sine qua non* for market entry, but without negotiation of appropriate reimbursement strategies market success and health system adoption are precluded. Due to the escalation of health-care costs and the increased pressure on healthcare budgets the time-to-market no longer means time-to-licensing but time-to-reimbursement [17, 18]. The market price of gene and cell based products is in the high range for the majority of the products, due to the high costs associated with the R&D, manufacturing, and clinical delivery, the relatively small market size and, for some gene therapy products, the potential to provide live-long clinical benefits with one single application (e.g. Glybera) [13]. As the granting of the marketing authorisation and the Health Technology Assessment (HTA) supporting decision making on pricing and reimbursement of a new medicinal product fall within the competence of different authorities, pharmaceutical companies have to comply with the dual requirements for regulatory approval and coverage and, therefore, have to understand and satisfy the needs and expectations of regulatory bodies and of the bodies performing the HTA. Whereas regulatory bodies base their decision primarily on the scientific assessment of the quality, safety, and efficacy and the evaluation of the benefit-risk profile of the medicinal product without taking into account economic considerations, reimbursement decision imply a cost-effectiveness analysis and are predominantly based on the assessment of the health benefits of the drug relative to existing treatment options [19]. Criteria for HTA vary between jurisdictions and in Europe HTA to support the decision on price and reimbursement is still performed at the national level, although

Europe-wide efforts for harmonisation in the HTA-field and collaborations between regulators and HTA organizations have been started in the last years [20, 21].

Data on comparative clinical effectiveness are often not available for GCT products, in particular in the case of therapies developed for the treatment of rare or orphan diseases.

Moreover, when a conditional marketing authorisation is granted, at the time of approval clinical trials are still ongoing. As a result, negotiations of reimbursement strategies have failed for many approved therapies, negatively impacting the market success of these products and resulting in market withdrawal for some of them. For instance, of the eight advanced therapy medicinal products approved so far in EU, only one (ChondroCelect) has achieved national reimbursement and only in three EU states [13, 22], and three of these products (MACI, Provenge, and ChondroCelect) have been suspended or withdrawn from the market for poor commercial performance [23-25].

Complicated administration procedures and adoption of advanced therapies. Administration of advanced therapies often entails complicated procedures requiring highly specialized technical training and associated to certain risks whose responsibility would fall on the treating physicians. This, together with the uncertainty of the coverage, may discourage the adoption of these therapies and result in the inability to reach and successfully treat a wider patient population [13, 18].

2. Regulatory framework governing gene and cell therapies in the European Union

2.1. Overview of the EU regulatory framework for advanced therapies

The current legal and regulatory framework for gene and cell therapy products in the European Union was established in 2007 with the Regulation 1394/2007/EC, which came into force in December 2008, placing under the same legal framework and defining as advanced therapy medicinal products (ATMP) three different classes of products, namely somatic cell therapy products (CTMP), gene therapy medicinal products (GTMP) and tissue engineered products (TEP) [26]. Before the enactment of the ATMP regulation, gene and cell therapy products have been regulated as medicinal products (MP) under Directive 2001/83/EC [27] as amended by Directive 2003/63/EC [28], while TEP remained outside any regulatory framework in most EU states. The lack of an EU-wide regulatory framework for these products led to divergent national approaches, hindering patients' access to these innovative treatments and affecting EU competitiveness in this key biotechnology area.

Key elements of the Regulation are:

- Inclusion of ATMPs under the mandatory scope of the centralized marketing authorisation procedure. This involves a single scientific evaluation of quality, safety, and efficacy of the

products carried out by the European Medicines Agency (EMA), leading to a single authorisation procedure valid throughout the entire EU;

- Establishment of a new multidisciplinary expert Committee, the Committee for Advanced Therapies (CAT), whose primary responsibility is to assess the quality, safety, and efficacy of ATMPs, and draft opinion of Marketing Authorisation Application (MAA) before they are discussed by the Committee for Human Medicinal Products (CHMP). The CAT also gives recommendations on the classification of ATMPs and reviews data on the manufacturing and testing of ATMPs developed by small companies. Other tasks of the CAT are related to the stimulation of scientific development and innovation in the field. The Committee is formed by representatives of all member states, physicians and patient organisations, and members of CHMP, to ensure flow of information and adequate collaboration.
- Establishment of technical requirements adapted to the particular characteristics of ATMPs. The regulation introduced a tailored approach for the evaluation, authorisation and post-authorisation follow up of these products and empowered the Commission to adopt specific requirements regarding the content of the MAA, good manufacturing practices (GMP), good clinical practices (GCP), and traceability of ATMPs;
- Provision of incentives for developers, both financial and in form or supporting procedures, to encourage research and development in the area of advanced therapies. Financial incentives consist in fee reductions for scientific advice and MAA. Special procedures to assist ATMP development include the procedures of ATMP classification and certification. Under the classification procedure, developers can request a scientific recommendation on the proper classification of their products and therefore gain certainty about the appropriate legal framework and guidance documents to refer to during the development. The certification procedure is restricted to the small and medium-sized enterprises (SMEs), which are often involved in the first stages of ATMP development but lack financial resources and/or regulatory expertise to move these products farther down the development pipeline. Goal of the procedure is to evaluate quality/manufacturing and, if available, preclinical aspects of the development of an ATMP, and to certificate the compliance with the relevant regulatory requirements in order to facilitate the transfer of the development of promising therapies to entities with the capability to translate them into medicinal products. Provisions governing the certification procedure are specified in the Commission Regulation (EC) 668/2009 [29];
- Introduction of the legal basis for the so called ‘Hospital Exemption’, which is specified in article 28 of the regulation and gives the member states the power to ‘exempt’ certain ATMPs from the obligation to obtain a central marketing authorisation and to authorize them at the national level under certain conditions (section 2.7).

Regulation (EC) 1394/2007 provided the legal basis for the adoption of specific requirements regarding the content of MAA, good manufacturing practice (GMP), good clinical practice (GCP), and traceability of ATMPs. Consequently, Annex I to Directive 2001/83/EC [27], which stipulates the technical requirements for all medicinal products, has been amended by the implementing Commission Directive 2009/120/EC [30] to include specific requirements regarding modules 3,4, and 5 of the MA dossier, documenting the quality and non-clinical and clinical development of MPs. Other significant amendments regard the Annex II to the EU GMP guideline, modified to contain specific adaptations for ATMP [31] and the draft guidance on GCP for ATMPs [32].
Other relevant legal documents to consider for the development and marketing of ATMPs include:

- Legislation on the requirements human cells and tissues used as starting materials (Directive 2004/23/EC [33], and its implementing directives [34, 35];
- Legislation concerning traceability and pharmacovigilance follow up (EC Commission Directive 2005/61/EC [36]);
- Legislation on genetically modified organisms (GMOs) (Commission Directive 2001/18/EC [37]);
- Legislation on medical devices applicable to combined ATMPs (Council Directive 93/42/EEC and council Directive 90/385/EC[38, 39]);
- Legislation on human blood and blood components used as starting material for ATMPs (Directive 2002/98/EC [40] and its implementing directives [41] [36].

In addition, all specific legislations on paediatric and orphan MPs, as well as on compliance with GMP and GCP and on post-authorisation and pharmacovigilance apply to ATMPs.

As defined by the regulation, ATMPs can be classified in four groups:

- *Gene therapy medicinal products*: biological MPs containing or consisting of a recombinant nucleic acid with a therapeutic, prophylactic or diagnostic effect related to the nucleic acid sequence or to product of genetic expression of this sequence;
- *Somatic cell therapy medicinal products*: biological MPs containing cells or tissues, which have been substantially manipulated or are not intended to be used for the same essential functions in the body, and are administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action;
- *Tissue-engineered products*: engineered cells or tissues to be used to repair, regenerate or replace human tissue;
- *Combined ATMPs*: products containing one or more medical devices, such as a matrix or scaffold, as an integral part of the MP and include viable cells or tissue parts or, in case of non-viable cellular/tissue parts, the primary mode of action is attributed to the cell

component as either pharmacological, immunological, metabolic or as repair, replacement, and regeneration.

Non-substantial manipulations are listed in Annex I of the Regulation and include *cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilisation, irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing, cryopreservation, and vitrification*.

2.2. Clinical trial authorisation and supervision

At present the regulatory oversight for clinical trials (CT) in the EU is responsibility of the individual Member States (MS) in which the clinical trials are to be conducted, in accordance with the national transposition of the provisions specified in the Directive 2001/20/EC, whose main goals were to harmonize the procedures governing CT in the EU and implement common Good Clinical Practice (GCP) standards and protection of CT subjects in all MS [42]. The clinical trial directive outlines the legal framework for the request of authorisation and review procedures. In addition, a detailed guidance on the contents of a clinical trial application to submit to the national competent authorities (NCA) is set out in the Communication from the Commission CT-1 [43]. However, divergent national transpositions and applications of the directive have led to the establishment of different procedures and partly different scientific requirements for approval between MS, leading to delays, increased administrative burden and costs, particularly for multinational CTs, creating a competitive disadvantage in running CTs in the EU. In response to this situation, the regulatory system has been revised and a new clinical trial Regulation [44] has been approved in April 2014. The new Regulation will replace the directive once the EU Clinical Trial Portal and Database, currently under development by the EMA, are fully operational. The Regulation, which has binding legal force in all MS of the EU enforces a central database and a coordinated review system intended to help streamline and simplify the authorisation and reporting procedures.

Until the Regulation replaces the Directive, the NCAs are responsible for the assessment of the application for investigational ATMPs (ATIMPs), as for all investigational medicinal products (IMPs), including evaluation of quality and manufacturing aspects, pre-clinical safety studies, and feasibility of clinical study design. The evaluation period can be extended for CT involving ATIMPs (90 days vs 60 days allowed for other MP; up to 180 days if external experts need to be consulted; no time limit for xenogeneic cell therapy) and explicit approval is required. In addition, CT protocols must be reviewed by an independent ethics committee. For multicentre trials, a positive single opinion achieved in accordance with the national system is required in each of the concerned MS. Hence for multinational trials involving several MS, sponsors must prepare and submit a separate application to the NCA and the Ethics Committee of each of the MS concerned. In the case of different opinions from NCAs and Ethics Committees, is responsibility of the

sponsor to address and reconcile the issues raised, resulting in a very burdensome and costly administrative process and significant delays in commencing the studies.

To address these issues, the Voluntary Harmonisation Procedure (VHP) was established in 2009 by the Clinical Trial Facilitation Group (CTFG) in the attempt to promote harmonisation of assessment decisions on multinational trial applications and administrative processes across the NCAs [45]. Under this procedure, applications for multinational CT are evaluated in a single procedure coordinated by a Reference NCA, resulting in a single scientific assessment and a joint discussion of all issues. Once a positive consensus is achieved (within 90 days for ATIMPs) the concerned NCAs have 10 days to approve the trial. Since its implementation, the VHP has been relatively successful with an increasing number of submissions every year. Since 2013 approximately 20 % of all multinational CT in the EU has undergone a VHP before the national submission [46], including several CT applications for ATIMPs [47]. However, not all MS take part to this voluntary procedure, the national phases can take longer than 10 days and the Ethics Committees are not involved in the procedure. Moreover, in the view of the pharmaceutical developers, the VHP has not been successfully adapted to handle the different national standards in the field of ATMP [48].

Similar harmonisation issues concern cells and tissues used as starting material and genetically modified organisms (GMO). The regulatory oversight of sourcing of human cells and tissues is governed in accordance with Directive 2004/23/EC and its implementing directives [33-35] but is nationally based, with different requirements for testing among the MS, which hamper the movement of starting materials across the EU. Similarly, the national implementation of the GMO Directive [37] has resulted in different requirements and timelines, making the integration of GMO assessment in CT authorisation particularly burdensome in the context of multinational CTs. As emerged during the multi-stakeholder meeting on advanced therapies convened by the EMA on 27 May 2016, these two areas urgently need to undergo a harmonisation process and require a more streamlined implementation of the relative Directives [49].

Scientific requirements for development of ATMPs are set in several guidelines issued by CAT and CHMP [50]. However, these documents provide guidance on the set of quality, non-clinical and clinical data at the level of MAA, and, with the exception of the document on non-clinical requirements for gene therapy products, no guidelines are currently available specifying requirements for application for clinical trials for ATMPs. The guideline on strategies to identify and mitigate risks for First-in-human clinical trials with IMPs applies to all new chemical and biological IMPs except gene and cell therapy MPs [51]. CAT is currently drafting a guidance document on the quality, non-clinical and where applicable clinical requirements for investigational ATIMP, taking into consideration guidance from other agencies (i.e. FDA and Health Canada) and experience from national clinical trials assessors and CTFG [52, 53]. The

guideline, which is expected to be released for consultation during the first quarter of 2017, will provide guidance for exploratory and pivotal CT but the main focus will be on the minimal requirements for early CT [53].

The structure of the application for a Clinical Trial Authorisation (CTA) is outlined in the Guidance CT1 and is the same for all MS, including a cover letter, a standardized application form, CT protocols, an Investigational Medicinal Product Dossier (IMPD) with data on quality and manufacturing, pharmacology/toxicology, clinical results and risk/benefit analysis, Ethics Committee opinion if already available, Scientific advice, and paediatric investigation plan (PIP) decision, if available. Additional MS-specific information may be requested by the NCAs in accordance with the national laws.

The methodology of the risk-based approach, an optional approach introduced by the regulation to increase flexibility (section 2.3), is encouraged from the early phase of development to scrutinize the critical process steps, identify risk factors inherent to the specific product and to develop a strategy to address and minimize the risks, ensuring the generation of a consistent product. As for all biological products, consistent manufacturing is deemed essential already in the early phases of clinical development, therefore identity, purity, safety and biological activity should be characterized as much as feasible in the different stages of development. Requirements regarding validation of analytical procedures and test release specifications are adapted to the stage of the clinical development, becoming more stringent toward the later phases, as scientific knowledge increases, often resulting in modification of the product. Potency, for instance, may not be conclusively addressed in the early stages, as correlation between potency and clinical efficacy can often be made only later in the development. Safety tests, conversely, should be validated already in the early stages. Due to the great variety of ATMP, case-by- case considerations apply [7, 47].

As for chemical based and biologic MP, a non-clinical evaluation is required for ATIMPs to address the potential toxicity and safety concerns, to demonstrate proof of principle, to establish safe doses for subsequent clinical studies, and to optimize route of administration. However, standardized programs may not be applied to these products and a tailored approach must be used to establish the safety profile of each one of them. Scientific justification must be provided for the choice of animal models and limitations of the model must be discussed. Omission of certain non-clinical studies may be considered when it is adequately justified by the findings obtained in POC studies or in *in vitro* tests [7].

GMP compliance is required in the EU for all medicinal products, including investigational products regardless the development stage, under Directive 2001/94/EC. A more flexible approach with less strict requirements during early development phases as well as a more

pragmatic approach to address process validation requirements have been required by both industry and academic stakeholders [49, 54]. The European Commission is currently revising the guideline on GMP requirements for ATMPs and launched a public consultation on the draft guidelines in 2016 [55].

Clinical trials have to be designed and conducted in accordance with the principles of good clinical practices. In 1996, the EU adopted the ICH E6 guidelines for GCP [56]. Additional draft guidelines have been developed by the EC to address specific issues related to GCP for CT involving ATMP [32].

2.3. Marketing authorisation application and approval procedures

The marketing authorisation of ATMPs falls within the mandatory scope of the centralized procedure, which leads to a single EU-wide MA granted by the EC after a single assessment process performed by the CAT/EMA. To be granted a MA, ATMPs have to fulfil the same scientific and regulatory requirements set for all MPs. Data on quality and manufacturing process, and on safety and efficacy supporting a positive benefit/risk profile must be provided, as well as information on risk management and risk mitigation.

Specific requirements for the MAA for each class of products are specified in the Annex I to Directive 2001/83/EC, as amended by Directive 2009/120/EC and take into account the specificity and heterogeneity of ATMPs. Further detailed information and guidance are provided to developers in specific guidelines developed by the EMA with the involvement of CAT and other Working Parties (WP), such as the Biologics WP (BWP), the Gene Therapy WP (GTWP), the Cell-Based Product WP (CPWP), the Safety WP (SWP), Efficacy WP (EWP), and Pharmacovigilance WP (PhWP), and published on the EMA website [50].

Despite the high-level technical requirements set for ATMPs to ensure an adequate level of public health protection, a certain grade of flexibility is allowed, in consideration of the specific nature of these products and the consequent additional challenges the developers are confronted with. Developers are indeed allowed to adopt a risk-based approach from the beginning and throughout the product development program, through the adoption of proportionate requirements based on risks. The legal basis for the risk-based approach, which is an optional approach, is provided by the amended Annex I, Part IV of Directive 2001/83/EC. Detailed information on implementation and methodology are outlined in a scientific guideline developed by EMA/CAT/CPWP [57]. This approach is based on the identification of the risk profile specific for each product, which is used to determine and justify the extent of quality, non-clinical and clinical data to be included in the MAA dossier.

2.4. Post-marketing requirements

All relevant legislation and guidelines regarding post-authorisation and pharmacovigilance requirements are applicable to ATMPs. In addition, EMA published an ATMP-specific guidance in accordance with Article 14 (4) of the ATMP Regulation, describing pharmacovigilance requirements, risk management planning, as well safety and efficacy follow-up [58]. Provisions that specifically apply to GTMP, CBTP and TEP are included in product-specific guidelines.

Additional post-marketing safety measures apply in consideration of additional risks associated to these products, including risks related to quality characteristics, storage and distribution of the product, administration procedures, interaction of the product and the patient (unwanted immunogenicity, intended and unintended genetic modification, et.), and persistence of the product in the patient. A risk management plan including information on the remaining risks and the measures to be taken post marketing for early detection of potential risks and effective mitigation must be included in the MAA. Gene therapy-related delayed adverse reactions have to be monitored through long-term follow-up of patients administered with authorized GTMP as well as patients enrolled in CT. Patient follow-up is recommended for at least 5 years for viral vectors without integration, latency or reactivation potential and much longer for integrating vectors.

Moreover, due to the characteristic and mode of actions of many of these products full efficacy assessment may need several years of follow-up and specific post-marketing obligations can be imposed. The generation of comprehensive data in a specific timeframe to confirm the positive risk-benefit balance is required in the case of a conditional MA (section 2.6.1).

2.5. Manufacturing and quality requirements

Utilisation of material of human origin (i.e. blood, tissues and cells) in the manufacture of ATMPs requires compliance with national legislation derived from the transposition of EU relevant directives, including Directive 2002/98/EC, Directive 2004/23/EC and their implementing directives, setting out requirements for procurement, donation and testing [33-35]. Manufacturing of ATMP must comply with Directive 2001/83/EC and with GMP guidelines [59]. Annex 2 (Manufacture of biological active substances and medicinal products for human use) set outs specific requirements for ATMPs [31].

Legally binding quality standards for all medicinal products in the EU and in the European Economic area are set out in the European Pharmacopoeia (Ph. Eur.) published by the European Directorate for the Quality of Medicine & HealthCare (EDQM) [60]. Compliance with Ph. Eur. requirements concerning raw materials, preparations, dosage forms, excipients, sterility methods, containers etc. when they exist is required. The Ph. Eur. contains several monographs and chapters relevant to ATMPs [61]. Notably to mention are two recently adopted chapters that

will be implemented in July 2017: the revised chapter 2.5.27 on the microbiological control of cellular products and the new general chapter on raw material of biological origin. The revised Chapter 2.5.27 on microbiological control of cellular products provides guidance on the best approaches to address the constraints associated with cell-based preparation such as short shelf-life and limited volume. The new general chapter on raw materials, developed in close collaboration with EMA, covers the quality requirements for raw materials of biological origin for the production of cell-based and gene therapy MP. Although non-mandatory, the chapter aims to harmonize the current practices, providing guidance on the identification of the critical quality attributes of raw materials, management of batch-to-batch variation and change control.

A traceability system must be in place allowing full traceability from cell donation and procurement to recipient through anonymous coding system.

2.6. Schemes and regulatory pathways to facilitate and expedite early access

In addition to the risk based approach introduced to provide flexibility to regulation of ATMPs, EMA has in place multiple regulatory mechanisms to enable early patient access to new promising medicines. These procedures are available for products and therapies that target an unmet medical need or address public health interests and are eligible for products authorised under the centralized procedure, including ATMPs [62, 63].

2.6.1. Conditional marketing authorisation

A conditional marketing authorisation may be granted to medicinal products for which comprehensive clinical data supporting safety and efficacy have not been supplied provided that the benefit/risk balance is positive, unmet medical needs will be fulfilled, and the benefit of an immediate availability of such products overweighs the risks of less complete data than normally required. The legal basis for the conditional marketing authorisation for medicinal products is stated in Article 14(7) of Regulation (EC) N0 726/2004 [64] and in Commission Regulation (EC) No 507/2006 [65]. Medicinal products are eligible if they are intended for treatment, prevention or diagnosis of seriously debilitating or life threatening diseases, have received orphan designation, or are to be used in emergency situation. Conditional MA, a temporary authorisation granted while the collection of comprehensive data is ongoing, is valid for one year on a renewable basis and it can be converted in a standard MA once the pending studies have been completed and data a positive benefit/risk profile are provided. Conditional MA is subject to specific post-marketing obligations, including the generation of comprehensive data in an agreed timeline. Applicants are advised to seek scientific advice or protocol assistance well in advance of a MAA submission [66]. Two ATMPs have been authorized so far under a conditional approval: Holoclar, a TEP based on autologous cells for the treatment of limbal stem cell deficiency due to ocular burns in adults [67] and Zalmoxis, a somatic cell therapy product containing allogeneic T-cells genetically modified to include a suicide gene used as adjunctive treatment in haploidentical

haematopoietic stem-cell transplantation for adult patients with high-risk haematological malignancies [68].

2.6.2. Marketing authorisation under exceptional circumstances

A marketing authorisation under exceptional circumstances may be granted when comprehensive data on efficacy and safety cannot be obtained due to the rarity of the indication or the inability to collect such data because of inadequate scientific knowledge or ethical issues. The legal basis is stated in Article 14(8) of Regulation (EC) No 726/2004 [64] and Directive 2001/83/EC Annex 1 [27]. Because of the impossibility to complete a full dossier, approval under exceptional circumstances can normally not be converted in a standard MA. Approval is subject to annual reassessment of the benefit/risk and to specific obligations, normally intended to address safety concerns. Glybera, an AAV-mediated in vivo gene therapy for the treatment of familial lipoprotein lipase deficiency, has been authorized under exceptional circumstances [69].

2.6.3. Accelerated assessment

Accelerated assessment procedure can be requested for innovative medicinal products expected to be of major public health interest (e.g. major impact on medical practice) and aims to reduce the timeframe for the evaluation of the MAA (from the standard 210 days to 150 days, without counting clock stops). The legal basis for accelerated assessment is provided in Article 14(9) of Regulation (EC) No 726/2004 [64]. Requests should be submitted two-months before MAA submission and should be preceded by a pre-submission meeting with the Agency, during which proposals for accelerated assessment can be discussed with rapporteurs from the CHMP and any other relevant committees [70].

2.6.4. Prime scheme; priority medicines

PRIME is a new scheme launched by the EMA in March 2016 to support the development of promising innovative medicines with the potential to benefit patients with no treatment options or to offer a major therapeutic advantage over existing treatments. PRIME fosters a better planning of medicine development making use of existing regulatory tools, such as scientific advice and accelerated assessment, and offering guidance on the overall development plan and regulatory strategy. Preliminary clinical evidences showing potential to benefit patients with unmet medical needs are required to support the application. Applicants from the academic sector and SMEs can apply on the basis of non-clinical data and tolerability data from a first-in-man clinical trial. Scientific advice in the early phases of development ensures optimisation of clinical trial designs and better uses of limited resources, including ensuring patients participation in clinical studies likely to provide the necessary data for a MAA [71, 72]. As of December 2016, 22 requests for PRIME eligibility concerning advanced therapies have been discussed and 7 ATMPs have been granted access to the PRIME scheme [73].

2.6.5. Adaptive pathways

Aim of the adaptive pathway approach is to balance the need for timely patient access to promising medicines with the need to collect adequate information on safety and efficacy of the medicines itself. This approach is based on existing regulatory processes, including scientific advice, compassionate use, conditional MA, and pharmacovigilance tools, such as patient registries, for the collection of real-life data. Same requirements and standards for the evaluation of benefit/risk profile and granting of MA apply as for any other medicinal product. However, a prospectively planned iterative approach is used, with approval in stages, followed by evidence gathering through real-life use and progressive licensing adaptions as more data become available. Adaptive pathways target medicinal products with the potential to address high medical needs, where evidence generation is challenging and large clinical trials would lead to enrolment of a considerable number of patients who would unlikely benefit from such treatments [74]. Iterative development can be obtained through a staggered approval, consisting in an initial approval for a restricted patient population followed by expansion of the indication or through an initial conditional approval based on surrogate endpoints followed by confirmation of the benefit/risk balance. Key features of this approach are the gathering of evidence through real-world data and early multi-stakeholder dialogue, involving not only developers and regulators, but also health technology assessment (HTA) bodies, health care professionals and patients in the discussion of the development program [75]. A pilot project has been run between March 2014 and August 2016. Of the 62 received applications, the majority were considered not suitable for adaptive pathways, 20 were accepted for a stage I meeting and 18 (including several ATMPs) were selected for a stage II, face-to-face meeting involving other stakeholders. At the end of the pilot one application progressed to a formal scientific advice and 6 to parallel advice from EMA and HTA bodies. Amongst these selected therapies, 3 are ATMPS, including a GTMP (LentiGlobin BB305 to treat beta-thalassemia, developed by Bluebird Bio [76]) and a CTMP (PLX-PAD placenta-derived cells for the treatment of critical limb ischemia under development by Pluristem [77, 78]). The pilot helped to identify aspects to be considered and improved in order to ensure timely and affordable access of patients to innovative medicines. These include a major involvement of patient organisations, definition of methodologically-sound strategies of real-world evidence collection and potential involvement of payers (i.e. entities responsible for decision on pricing and reimbursement on the basis of HTA body recommendations), which were not part of the pilot [79].

2.6.6. Scientific advice and consultation mechanisms

Early consultation with the regulatory authorities is deemed essential for the development of innovative new medicines, which pose scientific and regulatory challenges and it is one of the development support tools of adaptive pathways and PRIME approaches.

Several consultations mechanisms and opportunities are available to developers [80], including:

- scientific advice focused on development strategies, which can be requested at any stage of product development and is based on specific questions posed by companies;
- Protocol assistance, a form of scientific advice for developers of designated orphan medicines
- Parallel scientific advice with health-technology-assessment (HTA) bodies, which, through the simultaneous inputs from both parties, allows the optimisation of clinical evidences gathering to meet both regulatory and HTA requirements;
- Innovation Task Force (ITF), a multidisciplinary group established by the EMA in 2014 with the mandate to provide support to medicines innovation in EU, through engagement in early dialogue with applicants, in particular from SMEs and academic sectors, to identify scientific, technical and regulatory issues related to emerging therapies and technologies
- Parallel scientific advice with the Food and Drug Administration (section 5.1.2].

2.6.7. Orphan designation

ATMPs can be eligible for Orphan designation when fulfilling the criteria, which include the potential to diagnose, treat or prevent a life-threatening or chronically debilitating rare medical condition affecting no more than 5 in 10,000 individuals in the EU or for which there is no reasonable expectation that marketing of the product would generate sufficient return of investment. In addition, a therapeutic benefit over all existing marketed products for the same condition (clinical superiority) have to demonstrated. Financial and marketing incentives for the developers include fee reductions for regulatory activities, eligibility for protocol assistance and for accelerated assessment, administrative and procedural assistance for SMEs, access to research grants, and 10 years of market exclusivity for approved orphan products (extended to 12 if results from a paediatric investigation plan is submitted at the time of the MAA). Of the eight ATMPs approved in the EU, four have been granted orphan designation: Glybera, Holoclar, Strimvelis, and Zalmoxis [12, 67-69]. During the market exclusivity period, no similar medicinal product for the same therapeutic indication can be brought to the market. The concept of “similar medicinal products” in the context of the orphan legislation is currently under revision, to adapt the definition to technical and scientific innovations in the field of biological medicines including ATMPs. CAT is assisting the Commission and COMP in the definition of “Principal Molecular Structural Features (PMSF) for ATMPs [81].

2.7. Alternative access routes for patients to regenerative medicine products/therapies

In addition to the mandatory centralized marketing authorisation valid at Community level, Regulation (EC) No 1394/2007 introduced the possibility of an alternative regulatory pathway for ATMPs at national level under the competency of the national competent authorities. Article 28 of the Regulation empowers the member states to make “exceptions” and supervise and license the manufacturing and use of non-industrially manufactured ATMP, provided that these products

are used for individual patients in a hospital and under the professional responsibility of the treating physician. With the so called 'Hospital Exemption' (HE), these products are outside of the legal requirements set in the ATMP regulation and therefore do not need a MA. However, national requirements on quality, traceability, and pharmacovigilance equivalent to those required for the authorized medicinal products must be fulfilled. Moreover, ATMPs regulated under the hospital exemption can be produced and used only at national level. The scope of the HE is primarily to enable early access for innovative treatments under controlled conditions in situations of high medical needs and when no products have been authorized. In addition, HE aims to facilitate clinical research by non-profit organisations and to provide clinical experience, while potentially benefiting some of the patients, to support further development and future marketing authorisation applications. However, the different interpretation of the article 28 of the Regulation, especially regarding to the legally undefined terms 'nonroutine' and 'custom-made', has led to divergent implementations of HE in MP [47]. As emerged by the public consultation on the application of the ATMP Regulation conducted by the EC in 2013 (five years after the enactment of the Regulation), the diverse implementation of the HE across the EU has been identified by the stakeholders as a major issue [54]. A too broad use of the HE can deter the development of ATMPs with demonstrated quality, safety and clinical benefit and authorized at the community level, which have to face higher development costs and are subject to stricter requirements and obligations. This situation is deemed detrimental to public health, as a favourable benefit-risk balance is normally not available for HE products, systematic collection of safety and efficacy data is lacking or achieved only at national level, and the treatments are not available to all patients across the EU. Similar concerns have been raised at the multi-stakeholder meeting convened by the EMA on 27 May 2016, during which all participants agreed on the necessity to improve implementation of Article 28, through the harmonisation of criteria across the EU and clarification of the scope of the exemption, limiting its application to situations of high unmet medical need and where no authorized products are available. Stakeholders from both industry and academia called also for more transparency on the use of exemption products in each member state through the use of public registries and systematic collation of experience and safety and efficacy data from HE products [49].

ATMPs that are either subject of a marketing authorisation application or are undergoing clinical trials can be made available to patients under a compassionate use program, if they satisfy the criteria defined in Article 83 of Regulation 726/2004/EC ref, i.e. if they are intended for group of patients with life-threatening or seriously debilitating diseases and address an unmet medical need. Compassionate use programs are governed by individual Member States legislation. As for the HE, different national implementation has led to a big heterogeneity across Europe in terms of regulatory requirements and restrictions. For instance, many member states allow

compassionate use on a named/individual patient basis despite being clearly stated in the Regulation that it is intended only for group of patients [82, 83].

2.8. Current approved products and pipeline development trends

Since Regulation 1394/2007 came into force, 8 ATMPs have been authorized in the EU: 3 TEP (ChondroCelect and Maci for cartilage repair [14, 84], and Holoclar for treatment of limbal stem cell deficiency [67]), 2 in vivo GTMP (Glybera for treatment of LPL deficiency [69] and Imlygic for treatment of advanced melanoma [85]), one ex vivo gene therapy (Strimvelis for the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency [12]), one autologous somatic cell therapy (Provenge for treatment of advanced prostate cancer [11]), and one allogeneic somatic cell therapy for the adjunctive treatment in haploidentical haematopoietic stem cell transplantation in adults with high-risk haematological malignancies [68]). Three of these products have been withdrawn or suspended because of poor commercial performance (Maci, Provenge, and ChondroCelect). Details about these products are provided in Annex I, Table 1. Although these products have been granted a EU-wide marketing authorisation, decisions about prices and reimbursement are taken at a national level as a result of negotiation between MAH and governments, affecting the market access status in each MS. Indeed, the so far EC approved ATMPs are still facing national market access challenges (including unfavourable HTA assessments and payer reluctance to reimburse the therapies) and have not yet been authorized or commercialized in many EU countries [86].

A large number of ATMPs is under development in the EU, as demonstrated by CAT activities (219 scientific advice procedures, 237 classification procedures, 47 paediatric investigation plans as for December 2016 [73]) and the number of ongoing clinical trials, which has been consistently growing over the past 15 years. Hanna and co-authors [1] identified 54 clinical trials registered in 1999-2003, 333 in 2004-2010, and 572 in 2001-2015, with the 85% of the trials still ongoing. The majority of the trials are still in the early stages of development (64.3 % in Phase I and I/II and 27.9 % in Phase II and II/III) with only 6.9 % of the trial in Phase III. Somatic cell therapies are the most represented (53.6%), with TEPs and GTMP respectively at 22.8% and 22.4 % and combined products at 1.2 %. The dominant targeted therapeutic area is oncology (24.8%), followed by cardiovascular diseases (19.4%), inflammation (11.5 %), musculoskeletal system diseases (10.5%), and neurology (9.1%). The majority of the trials is sponsored by academia and non-for-profit organisations (73.2%). The involvement of commercial sponsors increases with the progression of the product development, rising from 20.5% of trials in Phase I or I/II to 53.8% of Phase III trials.

The majority of the projects are developed by academia and non-for-profit organisations (74,2 %). However, 71,4 % of the projects in late phases are developed by for-profit companies.

3. Regulatory framework governing gene and cell therapies in the United States

3.1. The US regulatory authorities and pharmaceutical law

The Food and Drug Administration (FDA) is the authority responsible for the regulation of medicinal products in the United States. The FDA is a federal regulatory agency within the Department of Health and Human Services which has the oversight for a wide range of products through the activity of separate centres. With regards to medicinal products and medical devices, the Center for Devices and Radiological Health (CDRH) regulates medical devices and radiation-emitting products, the Center for Drug Evaluation and Research (CDER) is responsible for regulatory oversight of prescription and over-the-counter chemical-based drugs and some biological therapeutics such as monoclonal antibodies and cytokines, and the Center for Biologics Evaluation and Research (CBER) has oversight over blood products, vaccines, and advanced therapies, including gene and cell therapies. Within the CBER, the Office for Cellular, Tissue and Gene Therapies (OCTGT) is responsible for Gene- and Cell-based therapies (GCT) [4, 8].

The US regulatory framework is based on:

- Statutes (Laws) passed by the Congress and signed by the President, which constitute the legal basis and provide FDA with the legal authority to regulate the aforementioned products
- Regulations, which implement and enforce the Statutes by providing details and interpretation of the laws
- Guidance documents, which reflect FDA interpretation of regulations, provide recommendations on compliance and, therefore, assist developers and FDA staff in the appropriate applications of regulations.

A comprehensive discussion of the Statutes within which FDA operates is available at the “Regulatory Information” page on the FDA website [87].

The Public Health Service Act (PHS Act) [88] and the Food, Drug, and Cosmetic Act (FD&C Act) [89] are the Statutes authorizing FDA to regulate human medical products as drugs, biologics or devices and defining product types.

Title 21 of the Code of Federal Regulations (CFR), available in a searchable format on the FDA website [90], specifies legally binding details on how the regulatory provisions set forth in the FD&C Act, PHS Act and in other relevant statutes are carried out by FDA.

Guidelines provide guidance on how to comply with the regulatory requirements and cover a wide range of topics and issues, including general regulatory activities broadly applicable to all medicinal products and topics relevant to specific indication or product types. Guidance documents are, however, not legally binding and developers are allowed to employ alternate approaches to satisfy FDA requirements [8].

3.2. US regulatory framework for advanced therapies

Gene and cell therapies are regulated in the US within the general framework for medicinal products and may be classified as biologic products, medical devices, "human cell, tissue, and cellular and tissue-based products" (HCT/P), or combination products, depending on the intended use, the composition or the mode of action, in accordance with the legal definitions provided by the FDA and presented in Table 3.1.

Table 3.1. Product definitions

Drug (FDCA section 201 (h), 21 USC 321(g)(1))	(A) articles recognized in the official US Pharmacopoeia, official Homeopathic Pharmacopoeia of the US, or the official National Formulary, or any supplement to any of them; (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 of any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (a), (B), or (C)
Biologic product (PHSA, section 351(i), 42 USC 262(i))	A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except chemically synthesized polypeptide), 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 USC 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 US Pharmacopoeia 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 [8]

The majority of GCT-based products are classified as biological products and are therefore regulated in agreement with Section 351 of PHS Act, which mandates that a biologics license is required prior their introduction into the market.

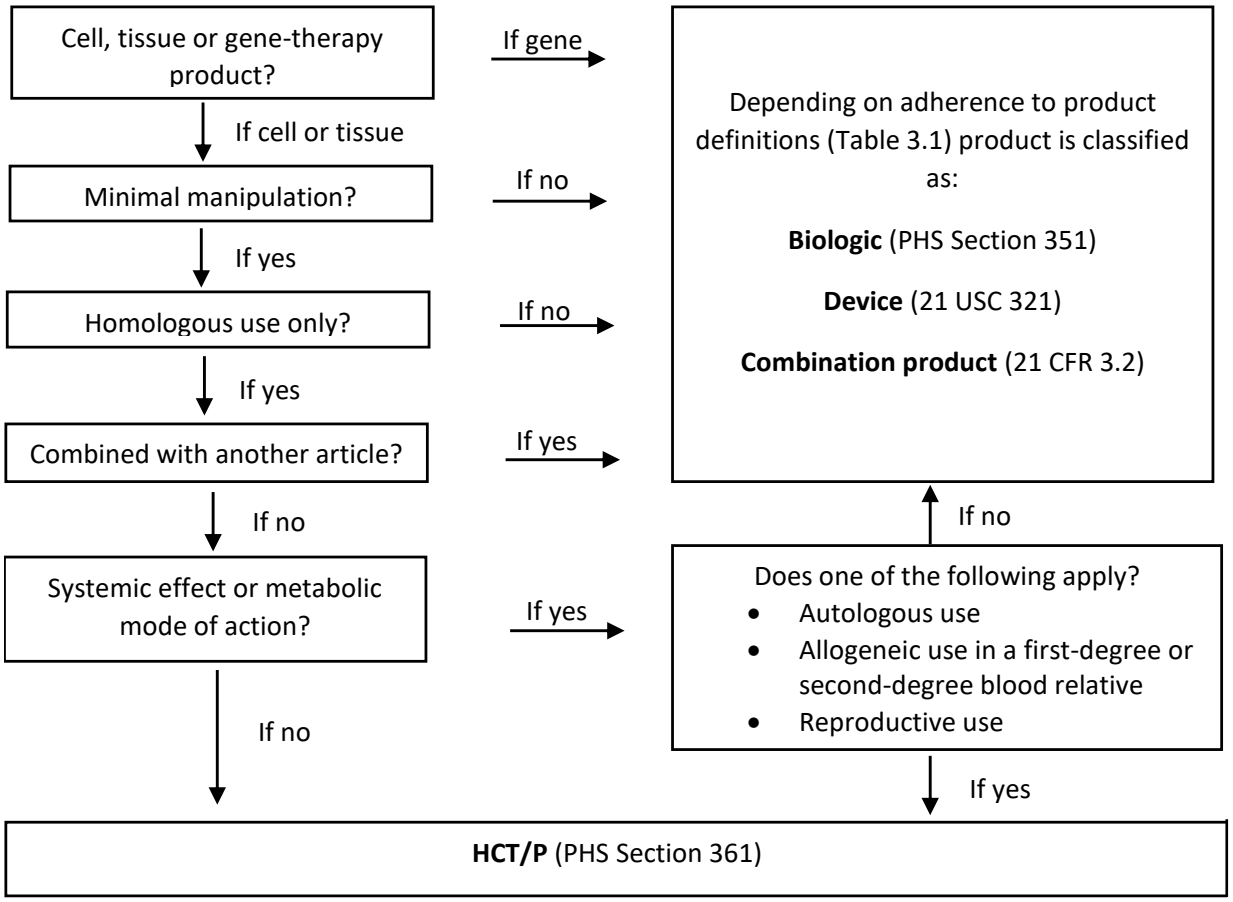
Products meeting the definition of HCT/P, i.e. articles containing or consisting of human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient, are subject also to additional regulations, namely the Tissue Rules (21 CFR 1271), introduced in 2005 to prevent the transmission and spread of communicable diseases. According to this regulation, HCT/P are classified and regulated through different regulatory pathways based on the risk level [8].

Products considered having a low risk are exempt from obtaining a pre-market approval and are regulated under Section 361 of PHS Act in addition to 21 CFR 1271. Classification criteria are defined in 21 CFR 1271.10 and include minimal manipulation, homologous use only, no combination with other articles, and absence of systemic effect or metabolic mode of action (section 4.3.1). These products are sometimes referred to as "361 HCT/P" [91].

Conversely, HCT/P that are more-than-minimally manipulated, or intended for non-homologous use, or are depending on metabolic action of living cells for their primary action are considered having a higher risk and are therefore regulated as Biologic or Device depending on adherence to product definitions. Cell- and tissue-based products classified as biologics are regulated under 21 CFR 1271 Parts A-D and under Section 351 of PHS Act and thus require a pre-market review and approval. These products may be referred to as "351 HCT/P" [91].

Combination products are products composed of different categories of regulated articles, such as biologic-device, biologic-drug, drug-device, and biologic-drug-device, provided that the different elements are intended for use together and each constituent is required for the intended metabolic effect.

Figure 3.1. Classification of GCT products



Adapted from European Commission: Study on the regulation of advanced therapies in selected jurisdictions [4]

GCT products can be classified as combination products when besides cell or gene components contain devices such as specific delivery devices (e.g., catheter for intra-arterial delivery of the product or spray devices), encapsulation/containment devices, and cell-scaffolds constructs. Following a Request for Designations (RFD), the Office of Combination Products (OCP) makes a formal determination of product classification, normally based on the primary mode of action, to determine the regulatory pathway and the jurisdiction within FDA for primary review responsibilities. Depending on the marketing strategy, a single or multiple applications may be necessary for a combination product [8, 91].

Several guidelines addressing specific aspects of development and authorisation of GCT products are in place and can be accessed through the FDA website [92].

An overview on the classification of GCT-based products is provided in fig 3-1.

3.3. Regulatory procedures for HCT products exempted from pre-market review and approval

Cell therapies regulated as HCT/Ps do not require pre-market review and are exempt from obtaining a marketing authorisation. As described in section 3.2, these products are regulated under Section 361 of PHS Act and through 21 CFR 1271.

As indicated in 21 CFR 1271.3(d), the main scope of this regulation is to prevent the spread of communicable diseases during implantation, transplantation, infusion, or transfer of human cells and tissues into human recipients.

The classification criteria are listed in 21 CFR 1271.10 as following:

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 tissue 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.*

Minimal manipulation is defined under 21 CFR 1271.3(f) 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.*

21 CFR 1271.3 provides examples of HCT/P (Table 3-1) and a list of articles that are not considered HCT/P:

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 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*

HCT/P are regulated through procedures and requirements specified in the regulation, including:

- Procedures for registration and listing (21 CFR 1271.21-37)
- Donor eligibility and testing (21 CFR 1271.45-90)
- Compliance with current Good Tissue Practice (GTP) (21 CFR 1271.150-320)
- Adverse reactions monitoring and reporting (21 CFR 1271.350).

3.4. Regulatory procedures for gene and cell therapy products regulated as biologics

3.4.1. Investigational use: clinical trial authorisation and supervision

The FDA oversees the entire lifecycle of drugs, biologics, and medical devices, from the investigational product development to post-marketing surveillance.

Section 505 of the FD&C Act and Section 351 of the PHS Act state that it is illegal to sell or distribute any medical product unless it is licensed or exempted. Investigational drugs, biologics and medical devices become exempted and can, therefore, been distributed and used for clinical studies, when an Investigational New Drug (IND) application (for drugs and biologics) or an Investigational Device Exemption (IDE) (for medical devices) are in effect.

Developers of GCT-based products regulated as biologics, which are the majority of these therapies, need to apply for an IND under the authority of the OCTGT, to formally request exemption from premarketing requirements, according to the procedures defined in 21 CFR 312, which are the same for chemical-based drugs and biologics.

21 CFR 312.23(a) specifies the requirements and the mandatory elements of an IND application, which include: application form; description of the general investigational plan; Investigator Brochure; detailed clinical protocol and informed consent; chemistry, manufacturing, and control

(CMC) information; pharmacology and toxicology data; and previous human experience information [8].

As indicated in 21 CFR 312.22, the primary objectives of IND review by the FDA are to assure the safety and rights of subjects and, in the later phases, to assure that the scientific design and evaluation are adequate to enable an evaluation of the product's safety and effectiveness. FDA review must be completed within the next 30 calendar days from the IND receipt date indicated together with the IND number on the acknowledgement letter issued by FDA upon receipt of an IND. After the 30-day review period, INDs become effective unless a clinical hold (i.e., an order to delay a proposed clinical investigation or to suspend an ongoing investigation) is imposed by the FDA and communicated to the applicant. In such a case, the proposed clinical trial may not proceed until the clinical hold issues are addressed.

All phase clinical trials require approval by the Institutional Review Board (IRB) (21 CFR 56.103 (a), an FDA-registered regulatory body in charge of reviewing and monitoring biomedical research involving human subjects with the aim to protect the rights and welfare of the participants in investigational research.

Prior to submission of an IND application for GCT products sponsors are requested to engage in a mandatory pre-IND meeting with the OCTGT (type B meeting according to FDA denomination), during which FDA provides non-binding feedbacks on specific questions related to and manufacturing, recommended animal studies, approaches to determine human dosing, clinical development scenarios and other potential issues. Early communication is strongly encouraged by FDA to accelerate the product development and streamline the IND application procedure [93].

Besides general guidelines assisting the developers in the preparation of an IND application (accessible through the FDA website [94]), specific guidance on the CMC section, on the preclinical assessment and on the design of Early-Phase Clinical Trials of investigational cellular and gene therapy products is provided in dedicated guidelines[95-98].

Taking into account the biological and technological complexity and heterogeneity of cell and gene therapy products, FDA applies a flexible regulatory approach and assesses CMC requirements on a case-by-case basis, considering, amongst other factors, the phase of product development. Regulatory requirements become progressively more stringent during the product development.

The CMC data to be included in an IND application are expected to demonstrate plausible safety of the proposed GCT product when administered to humans and comparability in product characterisation and biological activity to the product used in preclinical studies [8]. The required content for the CMC section is comprehensively described in the guidance documents

As for chemical based drug or biologic products, the pharmacology/toxicology section for an IND for GCT products must contain *in vitro* and *in vivo* animal data establishing an adequate scientific rationale and feasibility of the proposed clinical trial and supporting the initial safe dose for use of the product in human. Moreover, an adequate preclinical program should support the identification of active dose levels, starting dose and dose regimen, optimisation of the route of administration, characterisation of potential local and systemic toxicity, identification of patient eligibility criteria and of physiologic parameters for clinical monitoring [8, 99]. Although these preclinical testing objectives need to be met, flexibility is allowed and the evaluation and review is performed by the OCTGT based on a science-driven, product-specific benefit-risk analysis, which takes into account the product biological properties, the intended clinical application, target patient population, route of administration, and mode of delivery.
The OCTGT guideline on preclinical assessment of investigational cellular and gene therapy products provide guidance for the design of proof-of-concept (POC) and selection of suitable animal models, recommendations for safety/toxicology studies and guidance for testing strategy based on product specific properties [97].
Under 21 CFR 58, compliance with Good Laboratory Practice (GLP) is required for all preclinical studies. However, for GCT products some studies may be exempted [4, 97].

Detailed guidance is also provided by the FDA to address the scientific challenges and issues to consider when designing early-phase clinical trials, including first-in-human (FIH) Phase 1 studies (Guidance for Industry: considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene therapy Products [98]). This document addresses product specific issues, such as selection of the appropriate study population, dose determination and administration regimen, safety monitoring plan, and stopping rules.

Developers are also encouraged to submit to the FDA a Target Product Profile (TPP), consisting of a dynamic strategic summary of the overall intent of the clinical development program, including a statement of the desired outcome and the sponsor's intended labelling claim. The TPP facilitates the communication between sponsors the FDA and allows the sponsor to address potential issues early in the development [8].

Additional formal meetings with the FDA are held after completion of Phase I and phase II studies (end-of-Phase I, end-of-Phase 2 meetings, and pre-BLA meetings) to ensure that clinical trials design enables the generation of the necessary evidence of safety and effectiveness [100].

Late phase II and III clinical trials protocols have to be submitted after discussing the results of early phase clinical trials during the formal meeting with the FDA and are therefore evaluated separately from the initial IND application [4].

Clinical trials must be conducted in compliance with FDA's Regulation related to clinical trials and human subject protections [101]. FDA adheres to the ICH E6 Good Clinical Practice Guidelines (GCP) [56] and has incorporated aspects of the latest guidelines in many sections of the FDA regulations. IND application must include a GCP compliance certificate and a commitment of the sponsor, ensuring approval by an IRB for all proposed clinical trials [4].

3.4.2. Marketing authorisation application and approval procedures

Prior to introduction into interstate commerce within the United States, GCT products regulated as biologics requires a biologics license under section 351 of the PHS Act, which is issued after *"determination that the establishment(s) and the biological product meet the applicable requirement to ensure the continued safety, purity, and potency of such product"* (21 CFR 601.2(d)). Manufacturers need to submit an application for a Biologics License Application (BLA) to the FDA/CBER in accordance with the requirements specified under 21 CFR 601 [8]. The BLA needs to be submitted in electronic form structured in accordance with the Common Technical Document (CTD) of the ICH [102].

Implementation of GLP, GCP, and current Good Manufacturing Practices (CGMP) are required and the product must meet CMC standards for licensure through the BLA pathway. However, due to the product specific challenges, not all the requirements for a BLA are applicable to GCT products, since standardized manufacturing, quality, preclinical and clinical testing programs are often not applicable and product-specific testing programs must be co-developed before prior to licensure. Therefore, a flexible regulatory approach is employed by the FDA in the evaluation of the submitted scientific evidences.

BLA assessment is performed on a case-by-case basis taking in consideration the product characteristics, current scientific knowledge, the benefit-risk profile in the target population, and regulatory precedent experience with similar product or condition [8].

The FDA has issued many guidelines addressing the various issues specific to GCT to assist sponsor during the preparation of the BLA content and regulator during the assessment.

3.4.3. Post-marketing requirements

GCT products are subjected to post marketing requirements that apply to all drugs and biologics and are described in the guidance document: Guidance for Industry: Post-marketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug and cosmetic Act (July 2009) [103].

Post-marketing studies are categorized as Post-Marketing Requirements (PMR), which are studies or clinical trials the sponsor is required to conduct, and Post-Marketing Commitments (PMC), which are studies or clinical trials to which the sponsor commit but that are not legally required. PMR may be required to assess a known serious risk related to the use of the drug, to investigate signals of serious risk related to the use of the drug, or to identify unexpected serious

risks when available data indicated potential for such risks. PMR are required as a condition for approval in the following situations: a) to demonstrate clinical benefit for products approved under the accelerated approval procedure (21 CFR 314.510 for chemical-based drugs and 21 CFR 601.41 for biologics), b) in the case of deferred paediatric studies required under the Paediatric Research Equity Act (PREA) (21 CFR 314.55(b) for drugs and 21 CFR 601.27(b) for biologics), and c) to confirm safety and efficacy in humans for products approved under the Animal Efficacy Rule (i.e. approval relying on animal studies which have been proved to be a reliable indicator of efficacy in human) (21 CFR 314.510(b)(1) and 21 CFR 601.91(b)(1) [104]. Annual reporting is required for both PMR and PMC (Section 506B of the 21 CFR 314.81(b)(2) for drugs and 21 CFR 601.70 for biologics [105].

Gene therapy products are subjected to specific recommendations due to the potential delayed adverse events, including malignant formation, which could be caused by prolonged expression of transgenes or altered expression of endogenous genes. These delayed adverse events must be taken into account in the design of preclinical and clinical studies and long term follow up, which is recommended for a minimum of 15 years [106].

3.4.4. Manufacturing and quality requirements

As stipulated under 21 U.S.C. 351, manufacturing of all medicinal products must comply with current Good Manufacturing Practice (cGMP). As specified in CFR 210.2 cGMP requirements apply also to biological products, including GCT and HCT/Ps. In addition to general GMP regulations (21 CFR 210-211), specific provisions (21 CFR 600, 606, and 820) are applicable to biological products including GCT products.

Phase I trials are exempted from full compliance with Good Manufacturing Practice (GMP) [107]. GCT products must comply with Good Tissue Practice (GTP), implemented to guarantee not only quality and safety, but also detection and prevention of infectious diseases.

A product tracking system covering the entire development process, from the donor and starting material to the final disposition of the final product, must be in place [95, 96]. Traceability requirements are the same for GCT products and HCT/Ps (21 CFR 1271.290(b).

Standardized manufacturing and quality programs are often not applicable, and the most suitable testing assays must be established during development. Therefore, a flexible regulatory approach is applied during the development of GCTs, with regulatory requirements becoming increasingly more stringent in later phases of development as knowledge on product characteristics, manufacturing, and life cycles increases.

Despite the remarkable flexibility in the evaluation of the product specific testing methods, safety testing (including sterility testing and testing for the presence of replication-competent viruses for viral vector-based product), quality testing (including purity and identity testing and

evaluation of potency or biological activity), and characterisation testing (including evaluation of biochemical, biophysical, and/or genetic characteristics) are required upon BLA approval [8].
Donor eligibility and screening procedures are mandatory for non-autologous products and recommended for autologous products.

3.5. Schemes to facilitate development and early access to GCT products

3.5.1. Expedited clinical programs for serious or life-threatening conditions

The FDA has recently developed four regulatory pathways to facilitate the development and expedite the availability of drugs and biologics, including GCT products, intended to address unmet medical need in the treatment of a serious conditions while preserving adequate standards for safety and efficacy: Fast Track Designation, Breakthrough Therapy, Accelerated Approval, and Priority Review [108, 109].

3.5.1.1. Fast track designation

Fast track designation is aimed to facilitate the development and expedite the review of products that have the potential to fill unmet medical needs in serious conditions. The designation can be requested at any time of the development (with IND or after, but not later than the pre-BLA meeting). Potential to address unmet medical needs must be supported by clinical data when the request for designation is submitted during the late phases of the development. Designation may be granted on the basis of preclinical data when the request is submitted early in development.
Advantages of fast track designation include actions to expedite development and review, such as frequent interaction with the FDA during drug development, possible eligibility for Accelerated Approval and Priority Review of the BLA, and rolling review consisting of submission to FDA for review of sections of the BLA as they are completed.

3.5.1.2. Breakthrough therapy designation

A Breakthrough therapy designation has the goal to accelerate the development and review of products which may demonstrate substantial improvement on a clinical significant endpoint over available therapies. Request of designation, which should be submitted no later than the end-of phase 2 meeting, may be initiated earlier in development (with IND and after), but preliminary clinical evidence of treatment effect must be provided. Products receiving the designation are entitled to all benefits of Fast Track Designation plus intensive guidance on an efficient drug development program from phase 1 onwards, including organisational commitment involving senior FDA staff.

3.5.1.3. Accelerated approval

Accelerated approval is a marketing approval pathway for drugs intended to treat a serious condition and for which efficacy is demonstrated in adequate and well-controlled clinical studies

based on effects on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit or on evidence of an effect on a clinical benefit other than survival (legal framework: 21 CFR 314 (h) for NDA and 21 CFR 601(e) for BLA). Accelerated approval, called also "Approval under Subpart H" when concerns chemical based drugs and "Approval under Subpart E" when regards biologics, is a full approval under the law, but requires well-controlled post-marketing studies supporting clinical benefit (Phase-4 confirmatory trials). This approach may result in earlier access of new promising therapies to patients due to the faster collection of surrogate and intermediate clinical endpoints. The product approval may be withdrawn in the event that clinical benefits are not confirmed or are not sufficient to justify the risk associated with the product, or when confirmatory studies are not performed with the due diligence.

3.5.1.4. Priority review

Priority review designation may be assigned at the time of NDA or BLA filing to products intended to treat serious conditions, which, if approved, would provide a significant improvement in safety or effectiveness. Priority review consists of a shorter period for evaluation of a marketing application by the FDA, which commits to complete the NDA or BLA review in 6 months, instead of the 10 months required for standard review.

3.5.2. Scientific advice and consultation mechanisms

Gene and cell therapies are novel and complex products, which present manufacturing, scientific, and regulatory challenges because of their unique characteristics and heterogeneity. Due to their heterogeneity, standardized requirements and testing programs are often not applicable and product-specific procedures not yet available. Frequent communications between stakeholders and regulators are, therefore, necessary throughout drug development to meet these challenges and to optimize and accelerate product development.

Developers have the possibility to engage in formal meetings which are scheduled at critical points in the development process, such as before the submission of an IND application, at the end of Phase 1 and Phase 2, and pre-BLA meetings, when regulatory feedback is essential for the successful progression of the development program [8]. A CMC meeting focused on issues relating to production standards, stability, sterility, purity potency, scale up and comparability procedures is strongly recommended early in development. Additional information on meeting request and meeting preparation and procedures are provided in the dedicated guidance document [93]

A Special Protocol Assessment (SPA) can also be requested and it is strongly recommended to developers of GCT products when Phase 3 study protocol is submitted. Protocols eligible for SPAs are 1) animal carcinogenicity protocols, 2) final product stability protocols, and 3) protocols for phase 3 trials whose data will form the primary basis for an efficacy claim. Aim of this special assessment is to obtained a written agreement about critical aspects of trial design and an FDA

commitment to accept the study results for filing (unless public health concerns arise), but does not imply a commitment for BLA approval [110].

3.5.3. Orphan designation

Manufacturer of GCT products for rare disorders are eligible to apply for orphan drug designation. Criteria for designation, specified under the Orphan Drug Act and regulated under 21 CFR 316, include the potential to diagnose, treat or prevent a rare disease of condition that either affects less than 200,000 individuals in the US, or for which there is no reasonable expectation that costs of research and development can be recovered by sales. Orphan Designation is intended to encourage the pharmaceutical industry to develop medicinal products for rare diseases by providing financial benefits and marketing incentives for sponsors, including assistance in designing clinical studies, eligibility to apply for funding through the Orphan Products Grant Funding, tax credits for clinical research costs, waiver of BLA submission fees, and 7 year of market exclusivity for approved orphan products [8, 100].

3.5.4. Rare paediatric disease priority review voucher program

Under this program sponsor who receives an approval for a drug or biologic for a "rare paediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product [111].

3.6. Alternative access routes for patients to GCT products/therapies

As for all class of medicinal products in the US, GCT investigational products can be made available to patient outside clinical trials and marketing authorisation via the Expanded Access. Whereas the primary goal of clinical trials is to obtain information about the safety and effectiveness of a drug and, therefore, to serve the needs of the society and future patients (while benefit some of the participants), the purpose of expanded access is to serve the needs of patients with no therapeutic options, making promising treatments available as early as possible during the development process (treatment use rather than research purposes) [8, 112]. Three categories of expanded access are available [113]:

- Expanded access for individual patients, including for emergency use (21 CFR 312.310)
- Expanded access for intermediate-size patient population use (21 CFR 312.315)
- Expanded access for wide spread use under a treatment IND or treatment protocol (21 CFR 312.320).

Products intended to treat serious or life-threatening conditions for which there are no available satisfactory alternatives are eligible for expanded access programs if the potential benefit justifies the risks, provided that provision of the drug under this program will not interfere with the initiation, conduct, or completion of clinical investigation that could support marketing approval (21 CFR 312.305].

3.7. Current approved products and pipeline development trends

Excluding cord blood products, FDA has approved so far 7 GCT products as biologics (under PHS Act section 351): one in vivo gene therapy product (Imlygic for treatment of advanced melanoma), 4 autologous cellular products (Carticel and MACI for cartilage repair, Provenge for treatment of advanced prostate cancer, and Laviv-Azficel-T for the improvement of nasolabial fold wrinkles), one allogeneic cellular product (Gintuit for treatment of mucogingival conditions), and one biologic response modifier (Theracys-Bacillus-CalmetteGuerin live for treatment of carcinoma of the urinary bladder) [114]. Full description of these products is provided in Annex I, Table 2. In addition, two allogeneic cell-based therapies have been approved as class III medical devices (Apligraft, marketed as Gintuit for different applications, and Dermagraft) and one autologous cell-based therapy as humanitarian use device (Epicel) (Annex I, Table 3).

The study on the regulation of advanced therapies in selected jurisdictions commissioned by the EC [4] has identified 132 ongoing research projects (data lock point 31 December 2014), of which 88,6% in early phase of clinical development (Phase I, I/II or II) and the remaining in later phases (phase II/III or III). The most targeted disease areas include cardiovascular diseases (29.5%), oncology (21.2%), musculoskeletal system and connective tissue diseases (12.1%), and neurology (8.3%). The majority of the projects are developed by academia and non-for-profit organisations (74,2 %). However, 71,4 % of the projects in late phases are developed by for-profit companies.

4. Regulatory framework governing gene and cell therapies in Japan.

4.1. Japanese regulatory authorities and pharmaceutical law

Medicinal products are regulated in Japan under the responsibility of two Health Authorities: the Ministry of Health, Labour and Wealth (MHLW), and the Pharmaceuticals and Medical Devices Agency (PMDA).

The MHLW has the ultimate responsibilities in policies and administrative measures. The ministry has the authority to grant marketing authorisations to pharmaceuticals and medical devices, to issue post-marketing safety measures, and is responsible for direct product withdrawal following safety concerns. Within the MHLW, the Pharmaceutical and Food Safety Bureau (PFSB) undertakes the main duties of the ministry in the field of pharmaceutical regulatory affairs. Within the PFSB, the Medical Device and Regenerative Medicine Product Evaluation Division (MRED) is in charge of advanced therapies [115-117].

The PMDA, established as an independent administration agency in 2004, is the executive and operational agency. Its key services can be divided into three categories: relief services for Adverse Health Effects, post-marketing measures, and review. Amongst other tasks, the PMDA

is responsible for scientific evaluations for medicinal products and medical devices, GMP/GLP/GCP inspections, scientific advice on clinical trials, enhancement of safety measure and dialogues with sponsors. The PMDA consists of 25 offices, including several offices responsible for regulating differences classes of medicinal products and medical devices. Within the PMDA the Offices of New Drug I-V are responsible for chemical based drugs while the Office of Cellular and Tissue-based Product (OCTP) regulates advanced therapies [115, 118, 119].

The Japanese system of pharmaceutical law operates on four hierarchical regulatory levels (Annex II). The legal basis is provided by a national Act, Act of Pharmaceuticals and Medical Devices (PMD Act), which is implemented by two levels of legally binding regulations: enforcement ordinances issued by the cabinet (Cabinet ordinances) and enforcement regulations issued by the MHLW (ministerial ordinances). The last level of regulation consists of notifications or administrative letters describing specific measures and outlining non-binding guidelines. Notifications can be issued by the head of the PFSB, the head of Divisions (e.g. Evaluation and Licensing Division, Compliance Division or Safety Division) or by divisions within the PFSB [120] [116]. Guidelines and standards may also be promulgated as ministerial ordinances such as in the case of many guidelines relating to regenerative medicines.

4.2. Japanese regulatory frameworks governing clinical studies

The Japanese health research with human subjects includes interventional and non-interventional studies. Interventional studies are classified as clinical studies and includes both clinical research and clinical trials according to the following definitions [121]:

- *"Clinical study" refers to a study conducted to investigate the clinical efficacy and safety of an investigational therapy, including both clinical research and a clinical trial.*
- *"Clinical research" refers to a clinical study which is not intended to collect clinical data for a marketing authorisation application under the PMD Act. This type of study is conducted to gain scientific knowledge and establish various medical techniques*.
- *"Clinical trial" refers to a clinical study intended to be used to collect clinical data for a MAA under the PMD Act.*

Regulatory procedures, review systems and standards for application and conduct of clinical trials and clinical research are different. However, both types of studies must be notified to MHLW, which solely has the authority to permit to conduct clinical studies.

Clinical trials must comply with Japanese Good Clinical Practice (J-GCP) and local implementation of ICH-GCP [56, 121, 122].

In contrast, clinical research has lower data integrity standards and is not required to fulfil GCP standards. Nevertheless, the ethical conduct of the study and a certain level of subject safety must be ensured, as specified in the relevant guidelines.

For this reason, the results of clinical research may not be considered in the clinical data package for MAA, unless they fully comply this J-GCP [121].

Interventional treatments for patients are regulated by the Medical Service Act, the Medical Practitioners' Act, and the related law [121]. In addition, clinical trial for MA have to be conducted in compliance with the PMD Act, which stipulates that the first clinical trial protocol of any new product must undergo an intensive review by PMDA and MHLW within 30 days of application submission regardless the product category (pharmaceuticals, medical device or regenerative medicinal products). During this period, sponsors may be required to provide additional information and/or to modify the clinical trial protocol. However, all activities have to be completed within the 30 days review period, penalty the withdraw of the application [116, 123].

4.3. Japanese regulatory frameworks for advanced therapies

Following the discovery of induced pluripotent stem (iPS) cells by Shinya Yamanaka in 2006 [124], regenerative medicine and cell therapy have become a relevant component of the Japanese medical care system. However, prior to 2014 there were no statutory laws specifically regulating regenerative products, including stem cell therapies [125]. The Pharmaceutical Affairs Law (PAL), established in 1960 and revised in 2003 by introducing a biological products category [126], has regulated medicinal products, medical devices, quasi-drugs, and cosmetics, but was not suited for the characteristics of advanced therapies, which were classified as drugs or medical devices according to their primary mode of action. Outside the scope of the PAL Act, regenerative medicines and cell based products prepared within medical institutions and used for clinical research or medical treatment had been under the jurisdiction of the Medical Practitioners' Act and Medical Care Act, while clinical research using stem cells had been regulated by independent guidelines [127] [123]. With the aim to promote the development and to accelerate the introduction of regenerative medicinal products into the market, the Japanese Society for Regenerative medicine (JSRM) issued its "Yokohama Declaration" in June 2012, which called the Japanese Government for "appropriate regulatory approaches based on scientific rationales" and proposed a market-based scheme with post-hoc efficacy testing if safety is ensured at the stage of approval reviews [128, 129].

In response to the need for a specific and appropriate legislative framework, the Regenerative Medicine Promotion Law was enacted in May 2013, defining the responsibilities of the Japanese government for promoting the development of advanced therapies and their clinical application while ensuring patients' safety [130].

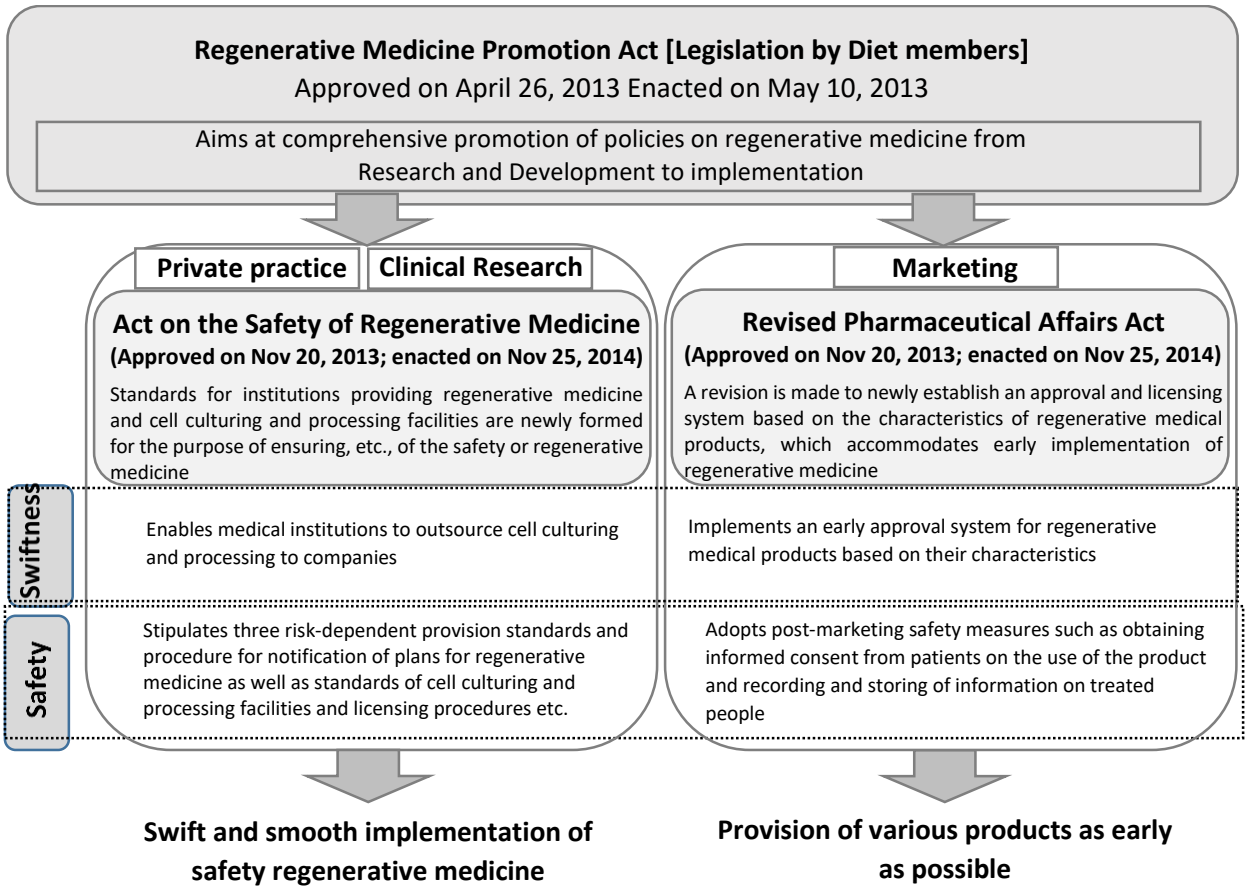
In line with this Law two related Acts regulating regenerative medicines, the Pharmaceutical and Medical Devices (PMD) Act, which is an amendment of the former Pharmaceutical Affairs Law (PAL), and the Act on the Safety of Regenerative Medicine (ASRM) were promulgated in November 2013 and came into effect in November 2014 [131, 132].

The new legislative framework has addressed the deficiencies of the previous system changing significantly the conditions for clinical application and approval process of regenerative medicine and is expected to facilitate and accelerate the development and commercialisation of new products and technologies.

These two acts define two different pathways to access to advanced medicinal products and treatments.

The PMD Act regulates regenerative medicine products developed and distributed by pharmaceutical companies after obtaining a marketing authorisation, while the ASRM regulates medical practice using regenerative medicine whose efficacy has not yet established and clinical research not intended for MA.

Figure 4.1. Institutional framework for promoting the implementation of regenerative medicine



Adapted from Tobita et al. [133]

The PMD Act, previously PAL, is the Japanese pharmaceutical law, which regulates manufacture, marketing, distribution, and use of pharmaceuticals, and medical devices. The revised Act establishes a specific pathway for regenerative medical products and introduces the option for a conditional and time-limited marketing approval, followed by a second approval procedure after seven years. The development of regenerative medical products is overseen by the PMDA, which

is also responsible for the scientific evaluation for the MA, while the MA is granted by the MHLW. The Act governs also clinical trials, i.e. clinical studies intended to collect clinical data for a MAA under the PMD Act, which require MHLW approval [134].

The ASRM, on the other hands, regulates the health research areas not covered by the PMD Act, including clinical research conducted to gain scientific knowledge or to establish medical techniques, and medical treatments using unauthorized regenerative medicine provided in medical institutions through an agreement between doctors and patients. The ARSM places this area of research and medical care under the direct responsibility of the MHLW, introduces licensing procedures, and stipulates quality control requirements for cell processing facilities. The new law aims to enhance patient access, while ensuring safety and adhesion to ethical principles [121].

4.4. Regulation of regenerative medicine under the PMD Act

The PMD Act is the revised Pharmaceutical Affairs Law in force since November 2014. The PMD Act has introduced two major changes to the approval system:

1) Introduction of a new product category, namely *regenerative medicine products*, including gene and cell therapy products, in addition to the existing categories of pharmaceutical products, medical devices, quasi drugs, and cosmetics
2) Stipulation of a conditional and time-limited marketing authorisation system, which is exclusively designed for the authorisation of regenerative medicine products, taking into account the distinct properties of human cell based therapeutics, such as the high degree of quality heterogeneity and small patient populations [121, 135].

The PMD Act is enforced through a number of separate legal documents, including Cabinet Ordinance (CO), MHLW Ministerial ordinance (MO), and MHLW Minister's Notification (MN), which are published by the Japanese government in Japanese only. In addition, administrative guidance documents issued by the MHLW and the PMDA provide description of consultation, application, and review procedures, while several guidelines issued by the MHLW specify further requirements related to product quality, safety, and efficacy or points to consider for the evaluation of specific products. An overview of relevant regulations and guidance documents is provided in Annex II.

4.4.1. Definition of regenerative medicine products under the PMD Act

The revised Pharmaceutical Affairs Act has introduced the definition of regenerative medicine products for the first time. However, depending on the purpose (MA or clinical research) advance therapies may be regulated under the PMD Act or the ARSM and this subdivision results in the generation of two legal definitions of regenerative medicine products in Japan [4]. The two definitions overlap almost entirely and closely adhere to the definition of advanced therapies

adopted in the United States and in the EU. A significant difference between the PMD Act and the ARSM concerns gene therapy products. While both in-vivo and ex-vivo gene therapy for MA fall within the scope of the PMD Act, only ex-vivo gene therapy products, which are handled as cell therapy, are regulated under ASRM. Clinical research with *ex-vivo* gene therapy is out of the scope of ASRM and is regulated under the Medical Care Act and Medical Practitioners Act [121]. The definition of regenerative medicinal products is provided in Article 2(9) of the PMD Act [120, 134]:

(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)

A further specification of the three classes of products regulated as regenerative medicinal products is outlined in Article 1-2 of the Cabinet Ordinance of the PMD Act [134]:

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

Moreover, the Ministerial Ordinance of the PMD Act provides a list of the categories of cell therapy and gene therapy products [135]:

Human cell processing products:
(1) human somatic cell processing products,
(2) human somatic stem cell processing products,
(3) human embryonic stem cell processing products,
(4) human artificial pluripotent cell processing products

Gene Therapy Products:
(1) Products derived from plasmid vectors
(2) Products derived from virus vectors
(3) Gene expression treatment products

Cellular therapy products are not further defined in the PMD Act and in the related Acts, however, administration of any "processed" living human or animal-derived cells is considered cell therapy in japan [121].

"Cell/Tissue processing" is defined in the "Guideline on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue" [120, 135]:

- *Artificial expansion/differentiation of cells and establishment of a cell line*
- *Pharmaceutical or chemical treatment to activate cells or tissue*
- *Modification of biological characteristics*
- *Combination with non-cell/non-tissue components*

- *Genetic modification of cells conducted for the purpose of treatment of diseases or for repair or reconstruction of tissues*

and does not include operations such as disintegration of tissue and separation of specific cells, treatment with antibiotics, washing, sterilisation by gamma irradiation, freezing, thawing and/or other procedures that do not use cells for the purpose of gaining different structures and functions from the original cells.

The minimal level of processing is essentially similar to "minimal manipulation" defined in the EU and US regulatory framework.

Established therapies, including organ transplantation, hematopoietic stem cell graft for homologous use, fertilized embryos and gamete for reproduction assistance medical care are not regulated as cell therapy and a MA is not required [135]. Blood and plasma-derived products are also out of the scope of the PMD Act. However, accordingly to the classification provided in the Cabinet ordinance, platelets derived from iPS cells are classified as "processed human cell products" and therefore regulated as a Regenerative Medicine Product rather than as blood derivatives [134].

Gene therapy is defined as the introduction of genetic material into the human body (*in vivo*) or administration of genetically modified cells into human (*ex vivo*) for therapeutic purposes [121]. Delivery of genetic material by means of both viral and non-viral vectors is considered gene therapy, while therapies using unmodified viruses used as vaccines, nucleic acid derivatives, RNA aptamers, and ribozymes are not categorized as gene therapy. Hence, siRNA and antisense oligonucleotides are not GT products, whereas vectors designed to express siRNA or antisense RNA are regulated as gene therapy. Under the PMD Act, both *in vivo* and *ex vivo* GT products intended for therapeutic purposes and developed to obtain a MA are regulated as regenerative medical products. In contrast, GT products developed for prophylactic use, such as vaccine vectors encoding antigens, are categorized as pharmaceutical products [135].

Cell therapy using genetically modified cells falls within both categories of CT and ex vivo GT products and are regulated accordingly [121].

4.4.2. Clinical trial authorisation and supervision

As for any other pharmaceutical products, before starting a clinical trial with a regenerative medicine product, sponsors are required to submit to MHLW a clinical trial notification (CTN), containing a clinical protocol, an investigator's brochure with an overview of the product characteristics and preclinical data, and material for informed consent. As mentioned in section 4.2 the CTN is reviewed by the PMDA and MHLW in an assessment period of 30 days (PMD Act Article 80-2) during which the sponsor may be required to provide additional information or to make the appropriate modifications. Taking into consideration the specific issues in terms of quality and safety of regenerative medicine product, the 30-day review period can be very

demanding. To support clinical application of these products, an early stage consultation program, named "Pharmaceutical Affairs Consultation on Research and Development" has been introduced in 2011 [123]. The new consultation program replaces the already existing pre-clinical review of quality and safety required since 1999 before submission of the first clinical protocol for regenerative medicine products. This mandatory consultation with the PMDA aims to ensure that all quality and safety requirements specified in the relevant guidelines are sufficiently met and is required before the CTN submission for the first clinical trial protocol for any regenerative medicine product. Unlike the CTN, the Pharmaceutical Affairs Consultation requires a review fee, as do all PMDA consultations for scientific advice. This is a one-time fee and a 90% discount may apply to academia and start-up-companies under specific conditions.

Regenerative medicine products targeting orphan diseases or other diseases in urgent need of innovative treatments are also eligible for prioritized consultation for clinical trial, which is one of the tools of the Sakigake Designation system (section 4.4.6.3)**.** This is a fast-track consultation and review program recently introduced by the MHLW to support and accelerate the early practical application for innovative medical products [123, 136, 137].

Following submission of CTN, the evaluation of safety and quality of the product is performed on a case-by-case basis taking into consideration product specifications, pre-clinical data, and starting material. Quality sections of the CTN should be prepared following the structure of Common Technical Document (CTD), with the appropriate deviations dictated by the specific characteristic of regenerative medicine products, which are specified in dedicated guidelines [4].

Compliance with J-GCP and local implementation of ICH-GCP is required for Clinical trials with regenerative medicinal products as for all clinical trials in Japan.

Full compliance with Good Gene, Cellular and Tissue-based Products Manufacturing Practice (GCTP), introduced with the revision of the Pharmaceutical Act as a new standard for manufacturing and quality control of regenerative in the industry, is not required during clinical trials [4, 134].

In compliance with GCP a review by an Institutional Review Board (IRB)/Independent Ethics Committee is required before the initiation of a clinical trial.

As stipulated by J-GCP specified national requirements, each site needs its own IRB and the site head has more responsibilities than what postulated in ICH-GCP, including obtaining IRB approval [4, 122]. GCP inspections are performed by the PMDA.

4.4.3. Marketing authorisation application and approval procedures

As any other pharmaceutical products, regenerative medicine products require marketing approval from the MHLW before being introduced into the Japanese market. As mentioned in section 4.4., with the revision of the Pharmaceutical Affairs Law a conditional time-limited

approval system has been established specifically for regenerative medicine products to enable earlier patients' access to these products.

This new approval pathway, outlined in Articles 23-26 of the PMD Act, provides a more flexible approach to safety and efficacy evaluation, in consideration of the difficulty and the long time required to evaluate the effectiveness these products [134].

According to this scheme, early approval with conditional and term limited licensing may be granted if the safety is confirmed and the efficacy can be assumed [138].

Demonstration of probable benefit can be supported by data based on surrogate endpoints obtained with exploratory clinical trials in relatively small and also heterogeneous patient groups [115, 134]. Accordingly, wider significance levels than those used in conventional trials may be acceptable during statistical analysis given the smaller and heterogeneous patient population. Moreover, study designs such as single arm clinical trial or observational studies may also be accepted in special cases [135].

During the conditional period follow up patient safety measures must be in place, including limitation of the sale destinations to clinical institutions with adequate knowledge and experience in regenerative medicine and obligation for the physician to keep a complete record on the administration of regenerative medicine products [138].

Other product specific conditions may apply. Conditional time limited approval is not automatically granted to any regenerative medicinal product. After evaluation of the submitted dossier PMDA/MHLW decide on a case-by case basis which type of approval is appropriate taking in consideration the target disease, the product specific characteristics, and the clinical relevance of the treatment in comparison with the pre-existing approved therapies.

Once this probationary MA is granted, products can enter the Japanese market, but confirmatory clinical data on safety and efficacy on clinical endpoints must be collected by means of large post-marketing clinical studies (typically phase III clinical trials) and an application dossier for a full approval must be submitted within no more than 7 years.

After this second review, a full approval may be granted. Product with unconfirmed effectiveness are withdrawn from the market and their approval is revoked.

4.4.4. Post-marketing and distribution control requirements

Basic post-marketing measures required for conventional pharmaceuticals, such as Good Post-Marketing Surveillance Practice or Good Post-Marketing Study Practice and Good Vigilance Practice (GVP) [139] [140] apply also to regenerative medicine products. As for traditional pharmaceuticals, re-examination to confirm safety and efficacy is required after a period of time set after the initial full approval (typically 8 years after the first MA for traditional pharmaceuticals)[117, 121]. Since 2013, sponsors are required to implement a Risk Management Plan, which includes a Pharmacovigilance Plan and a Risk Minimizing Plan [141].

Additional safety measures and post-marketing requirements specifically apply to regenerative medicine products to enhance patient safety, as follow [138]:

- Informed consent (PMD Act Article 68-4): Medical practitioners shall provide appropriate explanation and information on safety and efficiency to the patients and receive informed consent;
- Implementation of a traceability system (PMD Act Article 68-7): All stakeholders in the supply chain need to record and store information related to the patients to allow conducting survey and to ensure traceability in case of infections;
- Implementation of Post-marketing safety and efficacy surveillance (PDA Act Article 68-10, 68-13): MAH and physicians must report serious adverse events, infectious events and other safety issues to PMDA within a specific time frame;
- Submission of Periodic Infectious Disease Surveillance Reports related to the products and source material (PDA Article 68-14, 68-15);
- Inclusion of regenerative medical products under the umbrella of the Relief Services for Adverse Health Effects. Two relief fund systems are operated by PMDA with government subsidy and contributions from MAH based on annual sales (PMD Act Articles 19 and 21). The Adverse Reaction Relief Fund system is designed to compensate patients in case of any serious adverse events from the proper use of the products, while the Relief Fund system for Infections compensates patients suffering from infectious diseases transmitted by human- or animal-derived products (PMD Act Article 15);
- Implementation of user requirements for facilities and physicians: a license from local governments is required in addition to compliance with good distribution practice (GDP), building and facility standards, and human resources requirements (PMD Act article 40-5, 40-6, 40-7);
- Introduction of a patient registry: to facilitate management of conditional time-limited authorisations, to support long-term follow up and to help health care professionals to record and report post-marketing safety and efficacy data, MHLW/PMDA are developing a public national patient registry system, which will be maintained by PMDA [142].

4.4.5. Manufacturing and quality requirements

Several guidance documents issued by MHLW, some of which are legally binding, are in place to ensure quality and safety of regenerative products. A list of other relevant guidelines is provided in Annex II.

Amongst these, one of the most important is “Standards for Biological Ingredients” (amended and renamed as “Minimum Requirements for Biological Ingredients”), a ministerial notification covering regulation of human and animal-derived source materials, including manufacturing control and testing protocols for specific product classes, standards for the use of additives and

media components, and other relevant indications. Indeed, biological and regenerative medicinal products not in compliance with these standards are not allowed to be sold in Japan (PMD Act Article 65-6) [134].

In addition, the PMD Act has introduced a new standard for manufacturing management and quality control of regenerative medicine technologies and products, namely the Good gene, cellular, and tissue-based products manufacturing practice (GCTP), which addresses the unique aspects of regenerative medicine products and outlines specific quality system requirements for these products [135]. The aim of GCTP is to provide guidance on the identification of critical attributes, the definition of an appropriate quality target and the development of appropriate methods to continuously monitor and improve the manufacturing process, based on the control and acceptance of the risk for each product [115]. Process validation/verification, product quality monitoring, sterility assurance, prevention of cross-contamination, facility and equipment requirements, supplier control system, traceability for donors and raw materials are amongst the key aspects addressed by GCTP. In addition, the Drug Master File registration system for active pharmaceutical ingredients and raw materials, already in place in Japan since 2005 for drugs and medical devices, has been expanded in 2012 to include raw materials of regenerative medicine products, such as cells, media, medium additives and other relevant materials [123, 143]. Manufacturing and quality requirements are the same for autologous, allogeneic and xenogeneic cells [4].

Marketing authorisation holders are required to obtain a license from the local government (PMD Act Article 23-20, 81) and to have a responsible office in Japan. MAH need to comply with quality assurance standards (good quality practice), post-marketing safety standards (GVP), and human resource requirements as specified in the ministerial ordinance (PMD Act Article 23-21).

Domestic manufacturing sites must have a license granted by the MHLW, while foreign manufacturing sites are required to go through an accreditation procedure by the MHLW (PMD Act Article 23-22, 23-24). All manufacturing sites, domestic and foreign, must comply with GCTP building and facility standards, GCTP manufacturing and quality standards and human resources requirements (PMD Act Article 23-22, 23-24, 23-25) and are subject to inspection by PMDA (PMD Act Article 23-23) [134].

4.4.6. Scheme to facilitate development and early access

In addition to the expedited approval system under the PMD Act, based on a conditional, termed-limited authorisation, many other mechanisms are in place aimed to accelerate patient access to new promising regenerative therapies, including regulatory advice from early stages of development, orphan designation, priority review, and Sakigake designation system.

4.4.6.1. Scientific advice and consultation mechanisms

The PMDA offers various categories of consultations for scientific advice during the entire development process, including Pre-Phase I, Pre-Phase II and End of Phase II Meetings, Pre NDA Meeting, Prior Assessment Consultation (PAC), Assessment for designation of priority review, and Follow-up Consultation [116].

Constant communication between the sponsors and the PMDA are encouraged from early stages of development for regenerative medicine products.

As described in section 4.4.2., a "Pharmaceutical Affairs Consultation on Research and Development Strategy" with PMDA is required for any regenerative medicine product before submission of a Clinical Trial Notification. This mandatory consultation focus on the review of quality and pre-clinical studies, including examination of tumorigenicity and safety of biological ingredients, and scientific advice is provided on the design of early clinical trials, including definition of endpoints, and identification of patient population and sample sizes [115].

4.4.6.2. Orphan designation and priority review

As any conventional drug and medical device, regenerative medicine products developed for the treatment of life-threatening diseases and unmet medical needs are eligible for orphan drug status if they fulfil the orphan designation criteria, which include the rarity of the disease covered by the indication (medical condition affecting no more than 50,000 patients in Japan) and the excellent usefulness of the drug from a medical standpoint (PMD Act Article 77-2 and MHLW Ministerial Ordinance for the Enforcement of the PMD Act Article 251). Products with Orphan drug designation are entitled to various priority measures, including tax relief, financial aid, priority consultation and priority review (PMD Articles 77-3 and 77-4). Regenerative medicine products with orphan designation can receive priority review status (PMD Act Article 23-25(7)) and therefore obtain priority at each stage of the review process [117, 134]. Temcell, one of the two regenerative medical products approved under the new regulatory frame, has received orphan designation [144].

4.4.6.3. Sakigake designation system (Fast-track consultation and review program)

As part of the strategies to promote the development of innovative pharmaceuticals, medical devices and regenerative medicines, on June 2014 the MHLW announced the "Strategy of SAKIGAKE - Leading the world in the practical application of innovative medical products and devices", which is a strategy package "covering from basic research to clinical research/trials, approval reviews, safety measures, insurance coverage, improvements of infrastructure and the environment for corporate activities, and global expansion" [136] [123].

The goals of the strategy include:

- promotion and acceleration of R&D through supporting each stage (through strengthening the consultation system by PMDA, supporting orphan drug R&D, drug repositioning and

development of off-label, promoting public-private joint projects, supporting drug development and safety measures through Medical Information and Communication Technology);
- strengthening the structure of PMDA and improving the quality of Review and Safety Measures;
- improvements in the predictability of drug pricing system;
- enhancements in the infrastructure and environment for corporate activities (through strengthening industry competitiveness, supporting SME and venture enterprises, and improving the conditions for simultaneous international development);
- and promotion of regulatory science and harmonisation [137].

The core of the "Strategy of SAKIGAKE" consists of two policies:

- the SAKIGAKE designation system, which aims to facilitate R&D and to shorten the time to approval of medical products initially developed in Japan and with a prospective significant efficacy against diseases in urgent need of innovative therapy;
- the scheme for rapid authorisation of unapproved drugs, which expands the scope of the Council on unapproved drug/off-label use (previously limited only to products approved in EU or US) to products unapproved in Western countries, when satisfying certain conditions, and facilitates the environment for industries, with the aim to accelerate the practical application of unapproved/off-label use of drugs for serious and life-threatening diseases.

The SAKIGAKE designation system supports the R&D and the early practical application for innovative medicine products and therapies through:

1) consistent prioritized consultation by the PMDA which results in a shorter waiting time for a clinical trial consultation (1 month instead of the normal average 2 months-period);

2) substantial pre-application consultation, which consists of a *de facto* review before the application for approval;

3) prioritized review, aiming to a reduction in the total review period (6 months instead of the average 12 months-period);

4) assignment of a PMDA review manager, responsible for the overall management of the whole process toward approval, including conformity assurance, quality management, safety measures, and review;

5) strengthening post-marketing safety measures including the extension of the re-examination period.

Medical products developed for the treatment of diseases in urgent need of innovative therapy are eligible for the SAKIGAKE designation, provided that a prominent effectiveness can be expected based on the data of mechanism of action and early phase clinical trials and as long as

have been initially developed in Japan and an application for approval is anticipated to be submitted firstly or simultaneously in Japan. The designation procedure can be initiated by the applicant, with an application to be submitted to the Evaluation and Licensing Division (ELD) and to be reviewed by the PMDA, or by the ELD approaching a potential applicant [137, 145].
SAKIGAKE designation has been assigned in February 2016 to three regenerative medical products [146]:

- STR01, autologous bone marrow derived mesenchymal stem cell, developed by NIPRO Medical Co., ltd. for spinal cord injury patients (currently phase II CT)
- G47 Δ, Growth-controlled oncolytic herpes simplex virus type 1) developed by Daiichi Sankyo Co., Ltd. for malignant glioma (currently phase II CT)
- Autologous cardiac progenitor/stem cells, developed by Japan Regenerative Medicine Co., Ltd. for paediatric congenital heart disease (single ventricle physiology) (currently recruiting for phase III CT).

4.5. Alternative access routes for patients to regenerative medicine products/therapies

Apart from regenerative medicine products authorized under the PMD Act and clinical trials conducted to collect clinical data for a MAA and therefore regulated under the PMD Act, patients can have access to regenerative medicine therapies through the so called “clinical research”. In this context, clinical research is not intended for commercialisation and includes not only research in academic setting performed to gain scientific knowledge, but also treatments provided in medical institutions under physician discretion using regenerative medicine whose efficacy and safety have not been established in a formal approval process. Clinical research of regenerative medicine is regulated by the ASRM, described in detail in section 4.6.

Off-label use of approved regenerative medicine products as well as treatments resembling a regenerative medicine product already approved under the PMD Act are foreseen and regulated under the ASRM [4].

Moreover, investigational regenerative medicine products under clinical development can be made available to eligible patients outside of clinical trials under the compassionate use scheme, which has newly been incorporated into the PMD Act and came into effect in January 2016 [147]. The compassionate use program is intended for unapproved drugs under development in Japan for the treatment of serious and life threatening diseases with no effective authorized therapies available and concerns drugs in the final stage of development. It can be requested at the end of the confirmatory trial or when patient enrolment for pivotal trial is finished and it ends when a decision on the new drug application is taken. The program is intended for a group of patients in the form of an industry-sponsored trial and cannot be used on a named-patient basis.

As part of the efforts to facilitate and expedite access to unapproved medicinal products and devices a new framework has been enacted by the Japanese Diet and came into effect on 1 April 2016: a patient proposed health service (PPHS), under which a variety of drugs, regenerative medicine products and devices will be available regardless of their regulatory approval status around the world, provided that the treatment meets a certain level of safety and efficacy. The procedure is initiated by the patient, who makes an enquiry counter of one of 87 authorized hospitals (Medical Service Act-certified advanced treatment hospitals or Medical Service Act-certified clinical research core hospitals), which prepare the application documents, including protocol and informed consent forms approved by the institutional review board to be submitted to the MHLW. A decision is made within 6 weeks. Under this scheme, patients are enabled to purchase from abroad products already marketed in other countries and to access to unapproved drugs developed abroad. The service is provided as clinical research and the patients must pay the costs of medical products as well the costs of conducting clinical studies. This procedure is exceedingly burdensome for the core hospitals, which are in charge of tasks normally carried out by drug manufacturers, such as preparing protocol documentation, completing importation procedures and developing a reimbursement roadmap [147].

4.6. The Act on the Safety of Regenerative Medicines (ASRM)

The Act on Safety of Regenerative Medicines, promulgated in November 2013 and enacted in November 2014, established a regulatory framework for regenerative medicine, cell based therapies, including cancer immunotherapy, and gene therapies provided in clinical research other than clinical trials (normally performed in academic setting and in medical institutions for academic purposes) and in private medical practices under physician discretion. The main goal of the ASRM is to facilitate clinical studies and enhance patient access to innovative therapies while increasing safety in research setting [121]. The Act is implemented through the Cabinet Ordinance and the MHLW Ministerial Ordinance for the enforcement of the ASRM [134] [148, 149].

The ASRM and the related regulations specify requirements for medical institutions and physicians providing regenerative therapies and stipulates manufacturing and quality standards for cell processing facilities.

4.6.1. Definition of regenerative medicine under the ASRM

Regenerative medicines regulated under the ASRM are defined in article 2 of the Act as [134]:

Processed human or animal cells

(1) that are intended for either:

a) The reconstruction, repair, or formation of the structure or function of the human body;

b) The treatment or prevention of human diseases

(2) that are designated in the Cabinet Ordinance

The definition of regenerative medicine under ASRM overlaps with the legal definition introduced by the PMD Act, except for the fact that academic research with *in-vivo* gene therapy is out of the scope of the ASRM (4.4.1).

Article 1 of the Cabinet Ordinance provides a list of the therapies excluded from the scope of the Act, such as blood transfusion, hematopoietic stem cell transplantation, reproductive medicine as well as organ and tissue transplantation, if minimally manipulated. The definition of processing and minimal manipulation is the same for both Acts.

4.6.2. Clinical research authorisation and supervision: review scheme for the provision of regenerative medicine under the ARSM

Regenerative therapies and technologies are classified under the ARSM in three categories based on the potential risks which depend on the cell source, the type and extent of manipulation and the application [121] [134].

- Class I (high risk) includes induced pluripotent stem cell (iPS), embryonic stem cells, genetically modified cells, and allogeneic cells;
- Class II (intermediate risk) concerns most stem cell therapies other than class I and cell therapies for non-homologous use;
- Class III (low risk) includes cell therapies not qualifying for class I and II and not using stem cells or non-homologous cells.

Under the ASRM any plan for the provision of regenerative therapies regardless the risk category must be submitted to a Certified Committee for Regenerative Medicine for review and then notified to the MHLW. The certified committee, which can be inside or outside medical institutions, operate as an Institutional Review Board and is authorized to issue opinions on the provision plan, adverse advent reports and annual report. The requirements in terms of technical knowledge and reviewing experience are specified by the Act and are tailored on the complexity and risk associated to the therapy: risk class III products are evaluated by certified committees for regenerative medicine, whereas risk class II and I products must be reviewed by certified special committee for regenerative medicine, whose members need to have not only technical knowledge, but also experience with reviewing these applications (ARSM Article 7). Certifications are granted by the MHLW and are effective for 3 years (ASRM Article 28). To ensure an efficient implementation of the Act the MHLW subsidises the formation of Specially Certified Regenerative Medicine Committees by Clinical Research Core Hospitals [134].

In addition to the review by the special committees, class I (high risk) products undergo a formal approval procedure at MHLW, which will make a decision within 90 days based on the opinion of the Health Science Council (HSC), one of the advisory bodies of the Minister [133].

The provision plan must include a summary of the plan, description of the processed cells and research data related to similar treatments, quality control documents, contracts with external

processing facilities, informed consent procedures for recipients and donors (ASRM article 14), privacy protection provisions (ASRM Article 15), and, for applications concerning off-label use under the ASRM, the label of the marketed product.

Other requirements specified by the Act include record retention (ASRM Article 16), expedited reports for serious adverse events and submission of annual reports to the committee and the MHLW (ASRM Articles 17, 18, 20, and 21), and appropriate provision of indemnification for subject harmed as a result of participating in clinical research. The annual report must include information on the number of treated patients, incidence of diseases and disabilities resulted as a consequence of the treatment, and an overall evaluation of safety and scientific acceptability. This submission and reporting scheme is deemed by the MHLW an important step to ensure safety and to provide the minister with a comprehensive picture of the real status of regenerative medicine provision. A summary based on these reports is made public by the MHLW to guarantee transparency [121, 134].

As described in section 4.2, clinical research under the ASRM is not required to fully comply with J-GCP standards. However, to ensure an adequate level of safety and adhesion to ethical principles, the Act specifies requirements and standards to which providers must strictly adhere (ASRM Article 3-25). Although results obtained with clinical research are not admitted as part of a MAA, can be used to design confirmative clinical trials.

4.6.3. Manufacturing and quality requirements

Regenerative medicine regulated under ASRM are not required to comply with the minimum requirements set out in the guideline “Standards for Biological Ingredients” nor with GCTP requirements. However, the ASRM dictates standards for buildings and facility (Article 42) and for manufacturing and quality control (Article 44).

To increase quality and safety and to ensure a steady supply of the product, the ASRM has enabled the outsourcing of cell processing to companies specialized in cell culture outside medical institutions, previously considered an infringement of the PMD Act [133, 134]. Domestic cell processing facilities outside medical institutions must obtain a license from the MHLW Regional Bureau (ASRM Article 35), while foreign cell processing facilities require an accreditation from the MHLW (ASRM Article 39). Cell processing facilities inside medical institutions are only required to submit a notification to the MHLW Regional Bureau (ASRM Article 40). Confirmation of the quality of the processed cells from the processing facility is required (MHLW Ministerial Ordinance).

A summary of the requirements for the regulation of regenerative medicines under ASRM and PMD Act is provided in Table 4.1.

Table 4.1. Summary of regenerative medicine scheme under ASRM and PMD Act.

	ASRM		PMD Act	
Scheme	Clinical research	Medical treatment	Clinical trial	Medical treatment
Purpose	Research (not for marketing approval)	Medical treatment	Application for marketing approval	Medical treatment
Review requirements before clinical use	Certified IRB approval, MHLW submission, notification for class II and III, 90-day review for class I	Certified IRB approval, MHLW submission, notification for class II and III, 90-day review for class I	30-day review by MHLW/PMDA, IRB approval	MHLW marketing approval
Responsibility for safety and quality of regenerative medicine	Physician and medical institutions	Physician and medical institutions	Physician and medical institutions (investigator-initiated trial) or company (company-sponsored trial)	Company
Manufacturing facility registration	Notification (within medical institution) / license (outside medical institution in Japan) / accreditation (foreign)	Notification (within medical institution) / license (outside medical institution in Japan) / accreditation (foreign)	Not required	License (domestic) / accreditation (foreign)
Manufacturing facility requirements	ASRM Art 42,44	ASRM Art 42,44	GMP for investigational products	GCTP
Standards for clinical practice	Provider Rule (ASRM Art. 3 to 25)	Provider Rule (ASRM Art. 3 to 25)	GCP	Post-market safety requirements (PMD Act Art. 68-2 to 68-15)
National health insurance	Not covered (in principle)	Not covered (in principle)	Partially covered	Fully covered (in principle)

Adapted from Azuma K. [134]

4.7. Current approved products and pipeline development trends

Before the reform of the pharmaceutical law two advanced therapy products have been approved as medical devices: JACE (autologous cultured epidermis for the treatment of serious burns) in 2007 and JACC (autologous cultured cartilage for the relief of symptoms of traumatic cartilage deficiency) in 2012 [150]. Under the new regulatory framework two regenerative medical products have obtain MA in 2015: TEMCELL (human allogeneic bone marrow-derived mesenchymal stem cells for the treatment of acute graft versus-host disease) received full approval and orphan designation and HeartSheet (autologous skeletal myoblasts sheets for treatment of serious heart failure caused by ischemic heart disease) received conditional/time limited approval [151]. Full details about these products are provided in Annex 1, Table 4. Three products have received in February 2016 the Sakigake designation and are therefore eligible for priority reviews and fast-track drug approval (section 4.4.6.3). Conditionally approved regenerative medical products are eligible for reimbursement by the Japanese health system, which, however, requires up to 30% co-payment from patients [22, 129].

A study on the regulation of advanced therapies in selected jurisdictions commissioned by the EC [4] identified 131 ongoing research projects (data lock point 31 December 2014) targeting a

variety of medical conditions, including oncology (48 %), cardiovascular diseases (16.8%), musculoskeletal system and connective tissue diseases (8.4 %), and congenital malformations (5.3%). The majority of the projects (96,2%) are in the early phases of clinical development (phase I, I/II or II) and most of the developers are academia or non-for-profit companies (92,4%). However, in most cases these products are developed through partnerships between academia/non-for-profit organisations and for-profit companies, being the former responsible for the registration of clinical trials.

5. Global development and international harmonisation/convergence of regulatory approaches

The field of gene and cellular therapy is rapidly expanding worldwide and is affected by the increasing globalisation of medical product development. Several GCTs products have been authorized for marketing globally and both product development and clinical studies are increasingly conducted internationally.

Alongside the rapid scientific, technological, and clinical progresses which allow the generation of more and more complex products and the modification of the products already under clinical evaluation, the regulatory framework must be reshaped to face the challenges associated to these products in order to promote effective product development, guarantee the availability of safe and effective products to patients globally and protect the public health.

The regulatory framework for gene and cell therapies is at different stages in different jurisdictions, ranging from a quite mature, although still evolving status (such as in the US, the EU, in Canada, Chorea, Singapore and other countries), to newly established frameworks (such as in Japan, Taiwan and others).

In consideration of the global nature of product development, the growing number of clinical trials performed internationally, and the global marketing strategies, a prospective regulatory harmonisation and convergence is deemed paramount by both the global regulatory community and the industry. In addition to promote the sharing of information, and to facilitate the global marketing of GCT products, the development of common regulatory approaches addresses the risks to public health posed by tourism to countries lacking regulatory oversight and by access to the global market of products authorized by regulatory bodies with limited experience in the field.

Many initiatives aimed to establish common terminology and regulatory approaches, and to harmonize internationally recognized requirements have been undertaken in the recent years and many more are foreseen.

5.1. Standing interactions between regulatory authorities

Activities based on sharing and dissemination of information include, amongst others, the EMA-FDA-Health Canada ATMP cluster and EMA-FDA parallel scientific advice. Sharing of confidential information between regulatory authorities is made possible by arrangements such Confidentiality Commitments (CCs) and Memorandum of Understanding (MOU) [8] [152]. Bilateral cooperation between PMDA/MHLW and foreign regulatory authorities under confidential arrangements are also in place [153] .

5.1.1. EMA - US FDA - Health Canada ATMP Cluster

Clusters consist of regular meetings by phone or videoconference between regulatory agencies for discussion of specific matters of mutual interest [154] [155]. The ATMP cluster is a trilateral interaction between EMA, FDA, and Health Canada, with the aim to develop a reciprocal understanding of regulatory procedures, share documents and draft guidelines, and discuss engagement in workshops and advisory committee. ATMP cluster teleconferences are held five to six time a year and coincide with the CAT meetings.

5.1.2. US FDA – EMA Parallel Scientific Advice (PSA)

The parallel scientific advice program [156, 157] allows sponsors to seek joint advice with both agencies on specific scientific issues during the development phases of a specific MP, with the aim of optimizing product development by addressing divergence in requirements and avoiding duplication of efforts. Each agency provides independent advice and the focus is on sharing information and perspectives rather than harmonisation of requirements, which can be different.

5.2. Global strategies to promote regulatory convergence

5.2.1. International Pharmaceutical Regulators Forum (IPRF) Cell Therapy Working Group and IPRF Gene Therapy Working Group

IRPF promotes international cooperation activities between pharmaceutical regulators and is open to all regulatory authorities and regional harmonisation initiatives, such as the World Health Organisation (WHO), the Asia-Pacific Economic Cooperation (APEC), the Association of Southeast Asian Nations (ASEAN), and Pan American Health Organisation (PAHO) amongst others. A complete list of the regulatory authorities and organisations participating in IPRF meetings and activities is available on the IPRF website [158]. The purpose of the Forum is to promote sharing of scientific and regulatory expertise, facilitate discussions of emerging scientific developments and common challenges, identify the need for harmonisation and regulatory cooperation, and support international efforts towards harmonisation and regulatory convergence. These initiatives are currently in early stages and are focused on the mutual understanding of the regulatory landscape in the different countries/regions. Ongoing projects of the IRPF Gene Therapy and Cell Therapy working groups include a compilation of regulatory frameworks for

participating countries and a list of scientific and regulatory terminology used in each region in the gene therapy and cell therapy fields respectively [159] [160].

5.2.2. APEC Life Science Innovation Forum Regulatory Harmonisation Steering Committee

The Asia-Pacific Economic Cooperation established in 2002 the Life Science Innovation Forum (LSIF), a tripartite forum of government, industry, and academia, to create the right policy environment for life science innovation [161]. One of the objectives of the LSIF is to promote regulatory harmonisation in APEC economies aiming to achieve the maximum feasible level of convergence in the medical products sector by 2020. This task is carried out through the APEC Harmonisation Centre (AHC) and the LSIF Regulatory Harmonisation Steering Committee (RHSC). In 2011, Advanced therapies were identified as a priority working area within the scope of the APEC LSIF RHSC, leading to the development of the advanced therapy strategic roadmap endorsed by RHSC in 2013. The 'Roadmap to promote prospective regulatory convergence in cell- and tissue-based therapeutic products' is led by the Singapore Health Science Authority (HSA) and supported by the US FDA, Thailand FDA, Taiwan FDA, Korea FDA, Health Canada, EMA, and EDQM. The roadmap aims to establish a mutual and harmonized understanding of these products, establish training programs and information**,** exchange opportunities, and facilitate and implement strategies to promote prospective regulatory convergence [162]. In this context, regulatory convergence does not represent the harmonisation of laws and regulations, but is intended as a 'process whereby regulatory requirements across economies become more similar or aligned over time as a result of the gradual adoption of internationally recognized technical guidance documents and standards' [163].

5.2.3. Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S)

Focus of PIC/S are the development and promotion of high and harmonized GMP standards and guidance documents and training of Competent Authorities. Within the PIC/S the Expert Circle on Human Blood, Tissue, Cells & ATMPs is active in the field of blood, blood components, plasma derivatives, cells and tissues and, since 2015, ATMPs. Amongst the current goals of this circle is the development of guidelines and aide memoires for ATMP, including the elaboration of harmonized technical terms [164].

5.2.4. International regulatory forum on human cell therapy and gene therapy products

The Pharmaceutical and Medical Devices Agency and the Japanese Society for Regenerative Medicine jointly convened the International Regulatory Forum on Human Cell Therapy and Gene Therapy Products on March 16, 2016 in Osaka with support from Japan's Ministry of Health, Labour and Welfare, the National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), the Japanese Society of Regenerative Medicine (JSRM), the Forum for Innovative Regenerative Medicine (FIRM), and the Japan Pharmaceutical Manufacturers Association (JPMA) [165]. The forum brought together representatives from regulatory agencies (including PMDA,

US FDA, EMA, Health Canada, HSA Singapore, and other NCA in Europe and in Asia], academic institutions, and industry. In addition to promote dialogue between stakeholders at international level, the objective of the forum was the identification of critical scientific and regulatory issues to be addressed in view of global development of cell and gene therapy products [162]. At the end of the forum, it was agreed that international discussion on some critical issues (i.e. potency as quality attribute, challenges in raw material and impurity controls, relevance and feasibility of in vivo safety studies, tumorigenicity testing methods, and clinical studies design) should be continued and scientific alignment among international regulatory authorities should be pursued. However, regulatory convergence, rather than international consensus and guideline harmonisation, is deemed essential and feasible.

6. Discussion and conclusions

The comparison of the regulatory frameworks governing gene- and cell-based medicinal products in the three ICH jurisdictions reveals a high level of convergence. While in the US GCT products are regulated as biological products within the legal framework of medicinal products, in the EU and in Japan advanced therapies (ATMPs and regenerative medicine products respectively) are regulated within specific regulatory frameworks. In all three jurisdictions GCT products require an individual authorisation before being marketed.

The definition of “advanced therapies” is partially overlapping but not completely matching. The concept of regenerative medicine in Japan is substantially equivalent to the concept of ATMPs in the EU, with the difference that cell-based therapies can be included solely on the basis of more-than-minimal manipulation. In the US, the concept of gene and cell therapies is slightly broader, including in the category of cell-based products that require a marketing authorisation also minimally manipulated therapies for homologous use that have systemic effect and depend on their metabolic action for primary function.

In the EU and in the US a marketing authorisation is granted on the base of a positive benefit/risk profile supported by confirmatory quality, safety and efficacy data. However, the regulatory framework is specifically tailored to these innovative therapies and a flexible approach is applied: the product specific characteristics are taken into account and the type of evidences and studies to be submitted for marketing authorisation are decided on a case-by-case basis or in accordance with a risk-based approach, normally by means of frequent interactions between regulators and developers.

Japan has introduced in 2014 a new regulatory framework for regenerative medicines consisting of two different legislative acts and the corresponding regulatory approaches: a marketing authorisation pathway specific for regenerative medicine products manufactured and distributed by pharmaceutical companies, which is regulated under a dedicated section of the PMD Act, and a regulatory framework for academic research and clinical practice established by the Act on the

Safety of Regenerative Medicine. The regulation of the advanced therapies developed for the purpose of marketing is overall comparable to the frameworks existing in the EU and US. However, a new time-limited conditional approval pathway accessible only for regenerative medicine products has been introduced with the revision of the pharmaceutical legislation in 2014. This marketing authorisation pathway consists of a two-phased approval system with a conditional approval after demonstration of safety and probable benefit granting a marketing authorisation for a limited time (normally seven years) during which additional follow up patient safety measures are in place and confirmatory clinical data to support a positive benefit/risk profile must be collected and submitted to the national authorities for full marketing authorisation.

The quality and safety standards for biological products, including the elements specified in ICH guidelines Q5, Q6B, S6, and S7 [166, 167], generally apply to GCT products but there is a common understanding that the direct translation of the requirements for biologics is not applicable to many areas of advanced therapies. The majority of the overall regulatory approaches to evaluation of quality, safety and efficacy of these products are based on the current ICH guidelines in the three jurisdictions and present, therefore, a high grade of similarity. However, in order to provide the jurisdiction's interpretation of the legal framework, each authority has developed specific guidelines covering a variety of topics, including specification of manufacturing and quality standards, and considerations for preclinical and clinical study design.

Regulatory oversight of sourcing material, including provisions related to donor screening, donor testing and measures to ensure traceability, is in place in each jurisdiction to address the specific risks originated from using human or animal source material. However, these regulations are not harmonized across jurisdictions.

Quality requirements for raw material of biological origin are also not harmonized. Japan enforces specific standards and requirements for biological materials. Products violating these standards are not allowed to access the Japanese market. In the EU, an additional challenge is posed by lack of harmonisation among the different member states. The European Pharmacopoeia has recently published a general chapter on raw materials of biological origins for the production of cell-based and gene therapy medicinal products to foster harmonisation in quality standards and qualification practices.

In accordance with the ICH guidelines, compliance with GCP and GMP is required in all jurisdictions, but local implementation differences are present. Japan requires adherence to the principle of Good gene, Cellular and Tissue-based products manufacturing Practice (GCTP), which contains specific quality and manufacturing requirements for GCT products, which are more demanding compared to the requirements in other jurisdictions. Moreover, the extent of GMP compliance required before entering clinical trials differs among jurisdictions. While Japan and

the US apply more flexible requirements for early phases of the development, in Europe GMP compliance is required for all medicinal products, including investigational products, under Directive 2001/94/EC. However, a more flexible approach is under consideration and the European Commission is currently revising the guideline on GMP requirements for ATMP. In addition, guidelines on requirements for ATMP in early clinical trials are under development by CAT. A first consultation paper is expected to be released during the first quarter of 2017.

Another important difference between the jurisdictions concerns the regulatory oversight of clinical investigations. Whereas in the US and in Japan the same competent authority oversees the entire lifecycle of medicinal products, including investigational product development and marketing authorisation, in the EU the regulatory review and the decision on approval of clinical trials is a competency of each member state, while the review of MAAs is a pan-national competency and the decision on granting a MA is taken at Community level. This allocation of responsibilities hampers the rapid start of CTs in the EU, as different regulatory requirements for CTs are in place in different member states and for multicentre trials a separate application must be submitted in each country participating in the trial. This situation, which is perceived by developers as a competitive disadvantage in conducting clinical trials in the EU, will be improved and hopefully solved by the new regulation on clinical trials which will enforce harmonisation of the requirements in the EU for a more efficient clinical trial application process.

Similarly, the approval of medical devices is competence of the national authorities in the EU, resulting in additional administrative burden for the developers of combined ATMP.

All jurisdictions have regulatory pathways in place to expedite the development of advanced therapies and to decrease the time to marketing authorisation, enabling early patient access. Japan recently introduced a time-limited conditional approval pathway specifically for regenerative medicines. The new Japanese approval system sparkled a debate on the international scientific press and received several criticisms, as it was perceived as a subsidy of commercial clinical trials (whose expenses would be eventually covered by patients and the national insurance system instead of the developing company) and raised a concern about floods of unsuccessful treatments in the country [129, 168]. It was also suggested that ‘regulatory agencies around the world should resist pressure to create such fast-track systems’ [168]. However, as pointed out by representatives of the Japanese regulatory authorities and the Japanese scientific community [169, 170], the conditional and time-limited approval for regenerative medicines is consistent with the accelerated approval for serious or life threatening diseases established in the US by the FDA, which allows approval based on surrogate endpoints or clinical endpoints other than survival and is subject to post-marketing requirements, including the conduct of confirmatory studies. Carticel [171], a product based on cultured chondrocytes, was approved by the FDA in 1997 under this scheme. Similarly, EMA has recently introduced an

adaptive pathways approach, consisting in a prospectively planned marketing authorisation with conditions, based on existing procedures such as the conditional MA and MA authorisation under exceptional circumstances. The key features of this approach are an iterative development with staggered approval beginning with a restricted population, gathering of evidences through real-world data, and early multi-stakeholder (including HTA bodies) dialogue. Three ATMPs are in the adaptive pathways pilot project run by the EMA. Moreover, alternative MA pathways have been already used in the EU to ensure early access of ATMPs: Holoclar, a TEP derived by autologous limbal stem cells [67], and Zalmoxis, a somatic cell therapy product consisting of allogeneic T cells genetically modified to contain a suicide gene [68], were granted a conditional marketing authorisation in 2015 and 2016 respectively. Glybera, an AAV-mediated *in vivo* gene therapy, was authorized in 2012 under exceptional circumstances [69]. Further licensing flexibility and development support are provided in the US by other expedited clinical programs for serious or life-threatening conditions, including Fast Track and Breakthrough Therapy designations, in the EU by the PRIME scheme, and in Japan by the SAKIGAKE designation system. All these programs are based on an intensive use of scientific advice and consultation mechanisms provided by the regulatory agencies to foster a better planning of the overall medicine development and regulatory strategies, and on schemes to accelerate the review process. These approaches reflect a general regulatory trend in adapting licensing schemes to the challenges posed by advanced therapies, in order to improve timely access for patients. Conditional approval schemes, in place in all jurisdictions and increasingly foreseen for this class of products, especially for those targeting rare diseases, allow market access with relatively limited evidence. However, they present additional challenges. Efficient and robust post-approval surveillance systems must be in place. Moreover, conduct of pivotal post-marketing efficacy studies is challenged by patients' reluctance to enter a trial if they already have access to the therapy and unwillingness to be enrolled in the control arm of the study. Uncertainty about efficacy at the time of launch (and lack of alignment of evidence requirements) influence the health system payer decisions, generating a contradiction between the increasingly faster development and approval process promoted by the regulatory authorities and the challenges associated with health system adoption and market access for these therapies.

In all jurisdictions, advanced therapy products developed for the treatment of rare conditions can qualify for orphan designation and become eligible for orphan drugs incentives. Eligibility criteria are slightly different. Rarity of the disease and therapeutic benefit criteria are required in all three jurisdictions. However, prevalence for designation is less than 50.000 patients in Japan, less than 200.000 in the US and less than 5 in 10.000 in the EU. Insufficient return of investments is a qualifying criterion for EU and US. Additional restrictions apply in the EU, including seriousness of the disease (life-threatening or chronically debilitating condition) and the so called

"no satisfactory method" criterion according to which clinical superiority has to be demonstrated when other forms of treatment already exist for the same condition. Incentives are similar, including market exclusivity (10 years in the EU and Japan, 7 years in the US), tax credit, fee reduction, access to research grants, eligibility for tailored scientific advice and accelerated assessment (priority review in the US and Japan, eligibility for accelerated assessment in the EU). EMA and FDA have developed since 2007 common procedures for applying for orphan designation and for submitting annual reports on the status of development reducing the sponsor's administrative burden. EMA has also been engaged in collaborations with the MHLW and PMDA since 2010 to establish a mutual awareness regarding each other's procedures and to identify areas of similarity [172].

Besides participation in clinical trials and treatments with authorized products, advanced therapies are made available to eligible patients through different mechanisms in the different countries. In the US, the only accessible alternative route is the expanded access (similar to compassionate use in other jurisdictions), although it is implemented with different programs depending on the development stage of the drug, kind of protocol and number of patients to be treated. In contrast, Japan has recently introduced several mechanisms to enhance patient access, including the treatment in the context of 'clinical research' which is regulated under the Act on the Safety of Regenerative Medicine and is subject to less strict requirements. Clinical research includes research activities performed in academic setting and medical treatments provided in medical institutions under the responsibility of the treating physician. Off-label use of approved regenerative medicine products is also regulated under the ASRM. In addition, a compassionate use program, recently introduced under the PMD Act, regulates the use of investigational regenerative medicine products under clinical development. Under the Patient-Proposed Health Service scheme, patients are enabled to access products available abroad (marketed or unapproved), provided that a certain level of safety and efficacy are demonstrated. In the EU, besides the marketed ATMPs that are authorized and available at Community level, advanced therapies can be made available to patients at national level through the so called 'hospital exemption'. Under this clause, each member state has the authority to 'exempt' certain ATMPs from the obligation to obtain a centralized MA and allow their use within the national territory, provided that these products are prepared on a non-routine basis for individual patients and are administered in a hospital under the exclusive responsibility of a medical practitioner. However, the different implementation of the hospital exemption in the member states resulted in lack of harmonisation in criteria and requirements across the EU, causing great confusion for the developers and negatively impacting both patient access and the development of centrally authorized ATMPs. In addition, patients can access to ATMPs under development through compassionate use programs regulated at national level.

A summary of the comparison is provided in Annex III.

Despite the high level of harmonisation and regulatory convergence achieved by the ICH members, including similar approaches and regulatory procedures to accelerate the development and marketing of advanced therapies in line with the current global regulatory trends to enable early patient access, there is the perception amongst the developers and other stakeholders that the European regulatory framework for these products is less flexible and presents more burdensome requirements than in other jurisdictions.

This can partially be ascribed to the lack of a single global regulatory system operating in the EU. Whereas the marketing authorisation of advanced therapies is granted at Community level via a centralized procedure, several other functions are operated at national level under different regulatory systems, including the regulatory oversight for clinical trials and hospital exemption and the provisions regulating the starting material of biological origins and GMO requirements.

The EU risk-based approach is perceived by the developers as focus mainly on risks without giving the adequate consideration to expected benefits, particularly in situations of high medical need, whereas the US system is perceived with a less risk-averse attitude [4, 49]. In this context, a comparison with the Japanese regulatory framework is not possible, as, being only recently enacted, the impact of this new system on the timely availability of safe and effective advanced therapies cannot yet be measured.

Several aspects related to the development of advanced therapies, including GMP requirements in early development phases and regulations of raw material of biological origin among others, are still not fully harmonized across jurisdictions. Convergence in these areas is essential to implement successful mutual recognition schemes and to avoid delays in commercialisation of gene and cell based therapeutics.

Other factors recognized as hampering the development and availability of advance therapies are manufacturing constraints, lack of standardisation procedures and complex supply chains, stringent regulatory requirements, and difficulties in gaining reimbursement and market adoption. A necessary step to overcome the current manufacturing and scale-up/scale-out constraints is the promotion and adoption of more flexible manufacturing models, such as decentralized manufacturing, and innovative technologies based on increased automation and high-tech processing systems, such as closed systems and bedside manufacturing. These approaches, however, require a reshaping of the regulatory requirements and would benefit of more regulatory flexibility. Developers therefore call for a more flexible regulatory approach, especially in the EU, with a greater adaptation of the requirements to the developmental phase and risk categories and more pragmatic approach to process validation requirements. The excessively high cost of some of these products makes the reimbursement process and, as a

consequence, market adoption difficult to achieve. On the one hand, it is necessary to reduce costs through the development and implementation of less cost-intensive manufacturing technologies among other strategies. On the other hand, authorities should promote the adoption of reimbursement procedures tailored on the characteristics of these products, to accelerate availability of potentially high value therapies approved with limited clinical evidence. Innovative price and reimbursement models are under evaluation, including annuity payments, which spread the cost of therapies over an extended period of time, and risk-sharing programs or pay-for-performance, where payments are contingent on the product's clinical efficacy. For instance, a reimbursement model based on payment by instalment and by results has been negotiated by GSK with Italian authorities for Strimvelis [86]. In addition, efforts should be made to reach wider patient populations, increasing visibility and promoting the adoption of these products as standard-of-care for patients facing life-threatening diseases, for instance through early engagements of patient advocates and clinicians in the development process and adequate training for physicians to administer these treatments.

In the view of global development**,** many international initiatives have been initiated to promote regulatory science at global level and to develop regulatory convergence allowing the leverage of regulatory efforts (e.g. approvals by other reputable regulatory authorities) and minimizing duplication in regulations. Many of these initiatives are still at early stages and are currently involved in the identification of the factors hampering the development of advanced therapies and in the comparison of the different regulatory requirements, in the attempt to define the regulatory elements, which need to be aligned.

As emerged from the international regulatory forum on human cell therapy and gene therapy products in Osaka, further steps should be taken to increase regulatory convergence and minimize inconsistency, while promoting risk-based flexibility requirements. In line with this perspective it has been suggested to develop a Minimum Consensus Package (MCP) integrated by case-by-case approaches for the evaluation of substantially manipulated cell therapy products [173]. The MCP should be based on the common recognition among interested parties of the essential scientific and technological elements for CMC, pre-clinical and clinical studies applicable to most CTP and could be used as a common platform by all interested parties, for development, evaluation, and control. The MCP should be integrated by a flexible approach on a case-by-case basis, taking in consideration each product specific profile, target disease, development stage, experience with the use, and reflecting the continuous scientific and technological progress in the field.

As agreed by the global regulatory community a timely availability of safe and effective advanced therapies to patients can be achieved only through the coordination of international regulatory efforts and by promoting an internationally aligned regulatory environment based on mutual

recognition schemes and capable of efficient responses to the rapidly developing field while ensuring adequate standards.

7. Summary

Gene and cell therapy (GCT) products constitute a class of heterogeneous biopharmaceuticals with the potential to provide innovative treatments for a broad range of medical conditions for which conventional approaches have been proved inadequate.

Efforts have been made in many jurisdictions to establish a tailored regulatory approach in order to promote effective product development and to accelerate the practical applications of these innovative therapies, while ensuring public health protection. However, being these therapies in the frontline of a rapidly evolving field, a continuous reshaping of the regulatory framework is required to accommodate the improved scientific knowledge and technological progress.

The aim of this Master thesis is to compare the regulatory frameworks for gene and cell therapy products currently in force in the three ICH jurisdictions, namely Europe, the United States, and Japan. For this purpose, the regulatory pathways and specific requirements adopted by the different jurisdictions are analysed and discussed. Particular emphasis has been given to the strategies employed to address the challenges posed by this category of medicinal products and to the mechanisms to facilitate timely patient access to new innovative therapies. In addition, in the view of the increasingly global context of medicines development and regulation, this study includes an overview on the ongoing international initiatives to achieve regulatory harmonization/convergence in order to facilitate the global availability of safe and effective therapies in a timely manner.

The analysis of the three legal frameworks reveals a high level of regulatory convergence, along with differences and specificities. GCT products are regulated as biologics in the US, whereas in the EU and in Japan are regulated within specific regulatory frameworks. A tailored approach for regulating these products is deemed necessary in each jurisdiction, and the necessary flexibility is achieved by means of different regulatory tools. In the EU and in the US a marketing authorisation is generally granted on the base of confirmatory quality, safety and efficacy data supporting a positive benefit/risk profile. However, a flexible approach is applied and the type of evidences to be submitted is decided on a case-by-case basis in the US and in accordance with a risk-based approach in the EU. Japan has introduced in 2014 a new two-phased approval system for regenerative medicine, consisting of a time-limited conditional approval after demonstration of safety and probable benefit, followed by a full marketing authorisation after submission of confirmatory clinical data. Licensing schemes similar to the Japanese approval system for regenerative medicine products are available also in the EU (conditional approval and adaptive pathways) and in the US (accelerated approval) as tools to expedite the development of advanced therapies and to decrease the time to marketing authorisation. Additional specific

programs to provide further licensing flexibility and development support are available in all three jurisdictions, as well as mechanisms to make these therapies available to eligible patients besides participation in clinical trial and treatment with authorised products.

Although the overall regulatory approaches to evaluation of quality, safety and efficacy are based on the current ICH guidelines and present a high grade of similarity, several aspects related to the development of advanced therapies are still not fully harmonized across jurisdictions. For instance, quality requirements for biological materials and provisions related to donor screening and testing are region specific, and compliance with GCP and GMP is achieved with some local implementation differences. The extent of GMP compliance required before entering clinical trials differs among jurisdictions, with the more restrictive requirements present in the EU.

Interestingly, despite the high level of convergence achieved by the ICH members, there is the perception among developers and other stakeholders that the European regulatory framework for these products is less flexible and presents more burdensome requirements than in other jurisdictions. This can partially be ascribed to the lack of a single global regulatory system operating in the EU in regards to several functions (e.g. regulatory oversight of clinical trials and hospital exemption and provisions regulating starting material and GMO requirements), which are regulated at national level.

In view of the global development, a prospective regulatory harmonization and convergence is deemed paramount by both the regulatory community and the industry. With this purpose, many international initiatives have been initiated to promote regulatory science at global level and to harmonize internationally recognized requirements in the advanced therapies field.

As agreed by the global regulatory community, a timely availability of safe and effective gene and cell therapies will be achieved only through the coordination of international regulatory efforts and by promoting the development of common regulatory approaches capable of efficient responses to the rapidly developing field while ensuring adequate standards.

8. References

1. Hanna, E., et al., *Advanced therapy medicinal products: current and future perspectives.* J Mark Access Health Policy, 2016. **4**.
2. Trounson, A. and C. McDonald, *Stem Cell Therapies in Clinical Trials: Progress and Challenges.* Cell Stem Cell. **17**(1): p. 11-22.
3. Heathman, T.R., et al., *The translation of cell-based therapies: clinical landscape and manufacturing challenges.* Regen Med, 2015. **10**(1): p. 49-64.
4. EC. *Study on the regulation of advanced therapies in selected jurisdictions*. 2016; [cited January 2017] Available from: https://ec.europa.eu/health/sites/health/files/human-use/docs/20147306_rfs_chafea_2014_health_24_060516.pdf.
5. Ginn, S.L., et al., *Gene therapy clinical trials worldwide to 2012 - an update.* J Gene Med, 2013. **15**(2): p. 65-77.
6. Salmikangas, P., et al., *Manufacturing, characterization and control of cell-based medicinal products: challenging paradigms toward commercial use.* Regen Med, 2015. **10**(1): p. 65-78.
7. Salmikangas, P., et al., *Marketing Regulatory Oversight of Advanced Therapy Medicinal Products (ATMPs) in Europe: The EMA/CAT Perspective.* Adv Exp Med Biol, 2015. **871**: p. 103-30.
8. Bailey, A.M., et al., *United States Food and Drug Administration Regulation of Gene and Cell Therapies*, in *Regulatory Aspects of Gene Therapy and Cell Therapy Products: A Global Perspective*, M.C. Galli and M. Serabian, Editors. 2015, Springer International Publishing: Cham. p. 1-29.
9. Ridgway, A. *Potency assays for cell therapy products - International Regulatory Forum of Human Cell Therapy and Gene Therapy Products - Osaka, March 16, 2016*. [cited January 2017] Available from: https://www.pmda.go.jp/files/000211291.pdf.
10. McBlane, J. *Preclinical safety evaluation - International Regulatory Forum of Human Cell Therapy and Gene Therapy Products - Osaka, March 16, 2016*. [cited January 2017] Available from: https://www.pmda.go.jp/files/000211287.pdf.
11. EMA. *Provenge. European public assessment report*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002513/human_med_001680.jsp&mid=WC0b01ac058001d124.
12. EMA. *Strimvelis. European public assessment report*. 2016; [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003854/human_med_001985.jsp&mid=WC0b01ac058001d124.
13. Abou-El-Enein, M., A. Elsanhoury, and P. Reinke, *Overcoming Challenges Facing Advanced Therapies in the EU Market.* Cell Stem Cell, 2016. **19**(3): p. 293-7.
14. EMA. *ChondroCelect. European public assessment report*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000878/human_med_000698.jsp&mid=WC0b01ac058001d124.
15. Hourd, P., et al., *Regulatory challenges for the manufacture and scale-out of autologous cell therapies*, in *StemBook*. 2008: Cambridge (MA).
16. Hourd, P., et al., *Manufacturing models permitting roll out/scale out of clinically led autologous cell therapies: regulatory and scientific challenges for comparability.* Cytotherapy, 2014. **16**(8): p. 1033-47.
17. Eichler, H.-G., et al., *Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers.* Nat Rev Drug Discov, 2010. **9**(4): p. 277-291.
18. Dodson, B.P. and A.D. Levine, *Challenges in the translation and commercialization of cell therapies.* BMC Biotechnol, 2015. **15**: p. 70.
19. Henshall, C., et al., *Understanding the Role and Evidence Expectations of Health Technology Assessment and Coverage/Payer Bodies.* Therapeutic Innovation & Regulatory Science, 2014. **48**(3): p. 341-346.
20. *EUnetHTA. Organisation.*; [cited January 2017] Available from: http://www.eunethta.eu/about-us/organisation.

21. EC. *HTA Network Reflection Paper on "Synergies between Regulatory and HTA issues on Pharmaceuticals"*. 2016; [cited January 2017] Available from: https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/ev_20161110_co06_en.pdf.
22. Bubela, T., et al., *Bringing regenerative medicines to the clinic: the future for regulation and reimbursement.* Regen Med, 2015. **10**(7): p. 897-911.
23. EMA. *MACI: closure of EU manufacturing site*. 2014; [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Maci/human_referral_000380.jsp&mid=WC0b01ac05805c516f.
24. EMA. *Public statement on Provenge: withdrawal of the marketing authorisation in the European Union*. 2015; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2015/05/WC500186950.pdf.
25. EMA. *Public statement on ChondroCelect: Withdrawal of the marketing authorisation in the European Union*. 13 September 2016; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2016/08/WC500211564.pdf.
26. *Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.* Off J L 324:121-137, 2007.
27. *Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use.* Off J L 311:67, 2001.
28. *Commission Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use.* Off J L 159:46-94, 2003.
29. *Commission Regulation (EC) No 668/2009 implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises.* Off J L 194:7-10, 2009.
30. *Commission Directive 2009/120/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products.* Off J L243:3-12, 2009.
31. *EU guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use: Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use*. 2012; [cited January 2017] Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/vol4-an2__2012-06_en.pdf.
32. EC. *Detailed guidelines on good clinical practice specific to advanced therapy medicinal products* 2009; [cited January 2017] Available from: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/2009_11_03_guideline.pdf.
33. *Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissue and cells.* Off J L 102:48-58, 2004.
34. *Commission Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.* Off J L 38:40-52, 2006.
35. *Commission Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing preservation, storage and distribution of human tissues and cells* Off J L 294:32–50, 2006.
36. *Commission Directive 2005/61/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events* Off J L 256:32–40, 2005.

37. *Commission Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.* Off J L 106:1–38, 2001.
38. *Council Directive 93/42/EEC concerning medical devices.* Off J L 169:1–60 1993.
39. *Council Directive 90/385/EC on the approximation of the laws of the Member States relating to active implantable medical devices.* Off J L 189:17–52 1990.
40. *Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC.* Off J L 33: 30-40, 2002.
41. *Directive 2004/33/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.* Off J L 91:25-39, 2004.
42. *Directive 2001/20/EC of the European parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.* Off J L 121:34–44 2001.
43. *Communication from the Commission-detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1).* Off J L 82:1-19, 2010.
44. *Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC* Off J L 158:1–76, 2014.
45. HMA. *Clinical Trials Facilitation Group*. [cited January 2017] Available from: http://www.hma.eu/392.html.
46. HMA. *Clinical Trials Facilitation Group. Results of the Voluntary Harmonization Procedure 2009-2016*. 2016; [cited January 2017] Available from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2016_09_CTFG_Results_VHP_2009-2016.pdf.
47. Renner, M., et al., *Regulation of Clinical Trials with Advanced Therapy Medicinal Products in Germany.* Adv Exp Med Biol, 2015. **871**: p. 87-101.
48. Frankel, S.R. *Taking CAR T cells from First-in-man Trials to marketing authorisation - the view from a pharmaceutical developer - CAT Workshop: scientific and regulatory challenges of genetically modified cell-based cancer immunotherapy products - November 2016*. [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/12/WC500217507.pdf.
49. EMA. *Advanced therapy medicines: exploring solutions to foster development and expand patient access in Europe*. 2016; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/06/WC500208080.pdf.
50. EMA. *Guidelines relevant for advanced therapy medicinal products*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp.
51. EMEA/CHMP/SWP. *Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products EMEA/CHMP/SWP/28367/07*. 2007; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf.
52. EMA/CAT. *CAT work plan 2016*. [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2016/03/WC500203580.pdf.

53. Reischl, I. *Update on investigational ATMP concept paper guideline*. 2016; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/12/WC500218410.pdf.
54. *Report from the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004*. 2014; [cited January 2017] Available from: http://ec.europa.eu/health//sites/health/files/files/advtherapies/2014_atmp/atmp_en.pdf.
55. EC. *Summary of the responses to the targeted stakeholder consultation on the development of Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products pursuant to Article 5 of Regulation 1394/2007*. [cited January 2017] Available from: https://ec.europa.eu/health/human-use/advanced-therapies/2016_pc_atmp_en.
56. ICH. *Guideline for Good Clinical Practice - E6 (R1)*. [cited January 2017] Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
57. EMA/CAT/CPWP. *Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products (EMA/CAT/ CPWP/686637/2011)*. [cited December 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139748.pdf.
58. CHMP. *Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products*. [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf.
59. *Eudralex - volume 4 - Good Manufacturing Practice (GMP) guidelines*. [cited January 2017] Available from: http://ec.europa.eu/health/documents/eudralex/vol-4_en.
60. EDQM. *The European Pharmacopoeia - Background and Mission*. [cited January 2017] Available from: https://www.edqm.eu/en/european-pharmacopoeia-background-50.html.
61. Wicks, S. *European Directorate for the Quality of Medicines & HealthCare (EDQM) - International Regulatory Forum of Human Cell Therapy and Gene Therapy Products - Osaka, March 16, 2016*. [cited January 2017] Available from: https://www.pmda.go.jp/files/000211293.pdf.
62. EMA. *Support for early access*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000856.jsp&mid=WC0b01ac0580b18c78.
63. EMA. *Development support and regulatory tools for early access to medicines*. 2016; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/03/WC500202631.pdf.
64. *Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.* Off J L 136:1-70, 2004.
65. *Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.* Off J L 92:6-9, 2007.
66. EMA. *Conditional marketing authorisation*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp&mid=WC0b01ac05809f843b.
67. EMA. *Holoclar. European public assessment report*. 2015; [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002450/human_med_001844.jsp&mid=WC0b01ac058001d124.

68. EMA. *Zalmoxis. European public assessment report*. 2016; [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002801/human_med_002016.jsp&mid=WC0b01ac058001d124.
69. EMA. *Glybera. European public assessment report*. 2012; [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002145/human_med_001480.jsp&mid=WC0b01ac058001d124.
70. EMA. *Accelerated Assessment*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000955.jsp&mid=WC0b01ac05809f843a.
71. EMA. *PRIME - Priority Medicines*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439.
72. EMA. *Enhanced early dialogue to facilitate accelerated assessment of PRIority MEdicines (PRIME)*. 2016; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202636.pdf.
73. EMA/CAT. *CAT monthly report of application procedures, guidelines and related documents on advanced therapies - December 2016 meeting*. [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2017/01/WC500219367.pdf.
74. EMA. *Adaptive pathways*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce.
75. EMA. *Guidance for companies considering the adaptive pathways approach*. 2016; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196726.pdf.
76. *Bluebird Bio - press release - September 2015*. [cited January 2017] Available from: http://investor.bluebirdbio.com/phoenix.zhtml?c=251820&p=irol-newsArticle&ID=2049713.
77. *Pluristem Therapeutics - Clinical development strategy*. [cited January 2017] Available from: http://www.pluristem.com/clinical-development-strategy/.
78. GlobeNewswire. *Pluristem Receives Clearance from Germany to Initiate its Multinational Phase III Trial in Critical Limb Ischemia Targeting Early Conditional Marketing Approval*. 2017; [cited January 2017] Available from: https://globenewswire.com/news-release/2017/01/17/906163/0/en/Pluristem-Receives-Clearance-from-Germany-to-Initiate-its-Multinational-Phase-III-Trial-in-Critical-Limb-Ischemia-Targeting-Early-Conditional-Marketing-Approval.html.
79. EMA. *Final report on the adaptive pathways pilot*. 28 July 2016; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf.
80. EMA. *Scientific advice and protocol assistance*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9.
81. EC. *Concept of 'similar medicinal product' in the context of the Orphan Legislation: adaptation fo technical progress*. [cited January 2017] Available from: http://ec.europa.eu/health//sites/health/files/files/orphanmp/2016_07_pc_orphan/2016_07_consultation_paper.pdf.
82. Whitfield, K., et al., *Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries.* Trials, 2010. **11**: p. 104.
83. EFPIA. *Compassionate Use Systems in the EU - How to improve for early access to patients.* 2016; [cited January 2017] Available from:

http://ec.europa.eu/health//sites/health/files/files/committee/stamp/2016-03_stamp4/6_efpia_compassionate_use_presentation.pdf.
84. EMA. *MACI. European public assessment report*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002522/human_med_001660.jsp&mid=WC0b01ac058001d124.
85. EMA. *Imlygic. European public assessment report*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002771/human_med_001941.jsp&mid=WC0b01ac058001d124.
86. Dellamano, R., et al. *Advanced Therapy Medicinal Products (ATMPs) in Europe 8 years on: what is the path to makret access so far? - ISPOR 19th Annual European Congress - Vienna, 2016*. [cited February 2017] Available from: https://www.ispor.org/research_pdfs/54/pdffiles/PHP222.pdf
87. FDA. *Regulatory Information: Legislation*. [cited January 2017] Available from: http://www.fda.gov/RegulatoryInformation/default.htm.
88. *United States Public Health Service Act*. [cited January 2017] Available from: http://www.fda.gov/RegulatoryInformation/Legislation/ucm148717.htm.
89. *United States Federal Food, Drug, and Cosmetic Act (FD&C Act)*. [cited January 2017] Available from: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm.
90. *United States Code of Federal Regulations, title 21*. [cited January 2017] Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm.
91. Oh, S. *FDA's Perspectives on Cellular and Gene Therapy Regulation - International Regulatory Forum of Human Cell Therapy and Gene Therapy Products - Osaka, March 16, 2016*. [cited January 2017] Available from: https://www.pmda.go.jp/files/000211284.pdf.
92. FDA. *Cellular and Gene Therapy Guidances*. [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/.
93. FDA. *Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants*. 2009; [cited January 2017] Available from: http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf.
94. FDA. *Investigational New Drug (IND) Application*. [cited January 2017] Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm.
95. FDA. *Guidance for FDA Reviewers and Sponsors: content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene TherapyInvestigational NEw Drug Applications (INDs)*. 2008; [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072587.htm.
96. FDA. *Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Application (INDs)*. 2008; [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074131.htm.
97. FDA. *Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products*. 2013; [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm376136.htm.
98. FDA. *Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products*. 2015; [cited January 2017] Available from: https://www.fda.gov/downloads/Biologi.../UCM359073.pdf.

99. Bailey, A.M., M. Mendicino, and P. Au, *An FDA perspective on preclinical development of cell-based regenerative medicine products.* Nat Biotech, 2014. **32**(8): p. 721-723.
100. Takefman, D. and W. Bryan, *The State of Gene Therapies: The FDA Perspective.* Molecular Therapy. **20**(5): p. 877-878.
101. FDA. *Clinical Trials and Human Subject Protection - Regulations*. [cited January 2017] Available from: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm.
102. FDA. *Providing Regulatory Submission in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submission Using the eCTD Specifications Guidance for Industry*. 2015; [cited January 2017] Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.
103. FDA. *Guidance for Industry: Postmarketing Studies and clinical Trials - Implementation of Section 505 (o)(3) of the Federal Food, Drug, and Cosmetic Act*. 2011; [cited January 2017] Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172001.pdf.
104. FDA. *Postmarketing requirements and Commitments*. [cited January 2017] Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.
105. FDA. *Biologis Procedures (SOPPs) - SOPP 8413: Postmarketing Requirement/Commitment Related Submissions-Administrative Handling, REview, and CBER Reporting*. 2015; [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm223772.htm.
106. FDA. *Guidance for Industry: Gene Therapy clinical Trials - Observing Subjects for Delayed Adverse Events*. 2006; [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm.
107. FDA. *Guidance for Industry: CGMP for Phase 1 Investigational Drugs*. 2008; [cited January] Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070273.pdf.
108. FDA. *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*. [cited January 2017] Available from: http://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm.
109. FDA. *Guidance for Industry: Expedited Programs for Serious Condition-Drugs and Biologics*. 2014; [cited January 2017] Available from: http://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf.
110. FDA. *Guidance for Industry: Special Protocol Assessment*. 2002; [cited January 2017] Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080571.pdf.
111. FDA. *Rare Pediatric Disease Priority Review Voucher Program*. [cited January] Available from: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm.
112. FDA. *Guidance for Industry - Expanded Access to Investigational Drugs for Treatment Use - Qs & As*. 2016; [cited January 2017] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf.
113. FDA. *Expanded Access*. [cited January 2017] Available from: http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm.

114. FDA. *Cellular & Gene Therapy Products: Marketed Products*. [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/default.htm.
115. Sato, D. *Japanese regulation of regenerative medicine - ACTO Satellyte symposium - 2014*. [cited December 2016] Available from: https://www.pmda.go.jp/files/000199507.pdf.
116. Fiedler, B., *International Registration Procedures: Japan. MDRA-16. Module 3.* 2014.
117. *Japan Pharmaceutical Manufacturers Association (JPMA). Pharmaceutical and Regulations in Japan*. 2015; [cited December 2016] Available from: http://www.jpma.or.jp/english/parj/pdf/2015.pdf.
118. PMDA. *Services of PMDA*. [cited December 2016] Available from: https://www.pmda.go.jp/english/about-pmda/outline/0006.html
119. PMDA. *Organization*. [cited December 2016] Available from: http://www.pmda.go.jp/english/about-pmda/outline/0003.html
120. Kusakabe, T., *Regulatory perspectives of Japan.* Biologicals, 2015. **43**(5): p. 422-4.
121. Maeda, D., et al., *Regulatory Frameworks for Gene and Cell Therapies in Japan.* Adv Exp Med Biol, 2015. **871**: p. 147-62.
122. MHLW, *Japanese GCP. Ministerial Notification of MHLW; No. 28 [in Japanese].* 1997.
123. Azuma, K. and S. Yamanaka, *Recent policies that support clinical application of induced pluripotent stem cell-based regenerative therapies.* Regenerative Therapy, 2016. **4**: p. 36-47.
124. Takahashi, K. and S. Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors.* Cell. **126**(4): p. 663-676.
125. Konomi, K., et al., *New Japanese initiatives on stem cell therapies.* Cell Stem Cell, 2015. **16**(4): p. 350-2.
126. *Government of Japan. Act on the Partial Revision of the Pharmaceutical Affairs Law and the Blood Collection and Donation Service Control Act. Act No 96 [in Japanese].* 2002.
127. MHLW, *Guidelines for clinical research using human stem cells. 2006 MHLW Ministerial Notification No.425, 2010 MHLW Ministerial Notification No.380, 2013 MHLW Ministerial Notification No.317 [in Japanese].*
128. *Japanese Society for Regenerative Medicine. Yokohama Declaration 2012*. [cited December 2016] Available from: https://www.jsrm.jp/jokyhfxmf-123/#_123.
129. Sipp, D., *Conditional approval: Japan lowers the bar for regenerative medicine products.* Cell Stem Cell, 2015. **16**(4): p. 353-6.
130. *Government of Japan. Act for the Promotion of Regenerative Medicine Act No 13 of May 10, 2013 [in Japanese].*
131. *Government of Japan. The Act on the Partial Revision of the Pharmaceutical Affairs Law. Act No. 84 [in Japanese].* 2013.
132. *Government of Japan. The Act on Safety of Regenerative Medicine. Act No.85 [in Japanese].* 2013.
133. Tobita, M., et al., *Japan's challenges of translational regenerative medicine: Act on the safety of regenerative medicine.* Regenerative Therapy, 2016. **4**: p. 78-81.
134. Azuma, K., *Regulatory Landscape of Regenerative Medicine in Japan.* Current Stem Cell Reports, 2015. **1**(2): p. 118-128.
135. Okada, K., K. Koike, and Y. Sawa, *Consideration of and expectations for the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act in Japan.* Regenerative Therapy, 2015. **1**: p. 80-83.
136. MHLW, *Sakigake priority review designation pilot program for medical devices, in vitro diagnostics, and regenerative medicine products. MRED Director Notice 0701 No 1 [in Japanese].* 2015.
137. MHLW. *Strategy of Sakigake*. [cited December 2016] Available from: http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html.
138. MHLW. *Pharmaceuticals and Medical Devices. Policy information. Outline of the Law for Partial Revision of the Pharmaceutical Affairs Law (Act No.84 of 2013).* [cited December 2016] Available

from: : http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/150407-01.pdf.
139. PMDA. *GLP/GCP/GPSP Compliance Assessments*. [cited December 2016] Available from: : http://www.pmda.go.jp/english/review-services/glp-gcp-gpsp/0001.html.
140. MHLW/PFSD. *Good Vigilance Practice Ordinance to be complied by Marketing authorization Holders. PFSD/SD Notification No.1202-1*. [cited December 2016] Available from: http://www.pmda.go.jp/files/000153219.pdf.
141. Tawaragy, T. *New Streams of Risk Management - 27th DIA Annual EuroMeeting -Paris, April 2015*. [cited December 2016] Available from: http://www.pmda.go.jp/files/000204617.pdf.
142. MHLW, *Report of the committee on patient registry system of regenerative medicine products [in Japanese].* 2014.
143. MHLW, *Partial revision of "Guidance on the use of Drug Master File" Evaluation and Licensing Division (ELD) Director Notice 1228 No.27 [in Japanese].* 2012.
144. PMDA. *Temcell: review report*. [cited January 2017] Available from: https://www.pmda.go.jp/files/000215658.pdf.
145. Sato, D. *Updates on global movement in regulation of Advanced Therapeutic - Advanced Therapeutics Workshop CoRE - Singapore, January 13, 2016*. [cited December 2016] Available from: https://www.pmda.go.jp/files/000209780.pdf.
146. Sato, D. *Regulatory trends in regenerative medicine in Japan - International Regulatory Forum of Human Cell Therapy and Gene Therapy Products - Osaka, March 16, 2016*. [cited December 2016] Available from: https://www.pmda.go.jp/files/000211336.pdf.
147. Fujiwara, Y., *Evolution of frameworks for expediting access to new drugs in Japan.* Nat Rev Drug Discov, 2016. **15**(5): p. 293-294.
148. *Government of Japan. The Cabinet Ordinance for the enforcement of the Act on the Safety Regenerative Medicine. 2014 Cabinet Ordinance No. 278 [in Japanese].*
149. MHLW, *The Ministerial Ordinance for the enforcement of the Act on the Safety Regenerative Medicine. 2014 MHLW Ministerial Ordinance No. 110 [in Japanese].*
150. PMDA. *Medical Devices. List of approved products*. [cited Janurary 2017] Available from: https://www.pmda.go.jp/english/review-services/reviews/approved-information/devices/0001.html.
151. PMDA. *FY 2015 new Regenerative Medical Products*. [cited January 2017] Available from: https://www.pmda.go.jp/files/000214524.pdf.
152. Arcidiacono, J.A., J.W. Blair, and K.A. Benton, *US Food and Drug Administration international collaborations for cellular therapy product regulation.* Stem Cell Res Ther, 2012. **3**(5): p. 38.
153. PMDA. *Bilateral Cooperation*. [cited January 2017] Available from: https://www.pmda.go.jp/english/int-activities/bilateral/0003.html.
154. EMA. *Cluster activities*. [cited January 2017] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000655.jsp&mid=WC0b01ac0580953d98.
155. FDA. *Foreign Regulator Information Exchanges*. [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/InternationalActivities/ucm271098.htm.
156. EMA. *EMA - FDA Parallel Scientific Advice*. 2009; [cited January 2017] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf.
157. FDA. *SOPP 8001.6: Procedures for Parallel Scientific Advice with European Medicines Agency (EMA)*. 2013; [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm061218.htm.
158. *International Pharmaceutical Regulators Forum (IPRF)*. [cited January 2017] Available from: https://www.i-p-r-f.org/index.php/en/.
159. *International Pharmaceutical Regulators Forum (IPRF) - Cell Therapy Working Group*. [cited January 2017] Available from: https://www.i-p-r-f.org/index.php/en/working-groups/cell-therapy-working-group/.

160. *International Pharmaceutical Regulators Forum (IPRF) - Gene Therapy Working Group*. [cited January 2017] Available from: https://www.i-p-r-f.org/index.php/en/working-groups/gene-therapy-working-group/.
161. APEC. *Life Science Innovation Forum*. [cited January 2017] Available from: http://www.apec.org/Groups/Committee-on-Trade-and-Investment/Life-Sciences-Innovation-Forum.aspx.
162. Hayakawa, T., et al., *Report of the International Regulatory Forum on Human Cell Therapy and Gene Therapy Products.* Biologicals, 2016. **44**(5): p. 467-79.
163. Kellathur, S. *Cell- and tissue-based therapeutic product regulations in Singapore and regulatory convergence - International Regulatory Forum of Human Cell Therapy and Gene Therapy Products - Osaka, March 16, 2016*. [cited January 2017] Available from: https://www.pmda.go.jp/files/000211377.pdf.
164. *Pharmaceutical Inspection Co-operation Scheme - PIC/S Expert Circle on Human Blood, Tissues, Cells & ATMPs*. [cited January 2017] Available from: https://www.picscheme.org/en/pia-pic-s-training-expert-circles-training-human-blood-tissues-cells-atmps.
165. PMDA. *International Regulatory Forum of Human Cell Therapy and Gene Therapy Products - Osaka, March 16, 2016*. [cited January 2017] Available from: https://www.pmda.go.jp/review-services/symposia/0050.html.
166. ICH. *Quality Guidelines*. [cited January 2017] Available from: http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.
167. ICH. *Safety Guidelines*. [cited January 2017] Available from: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html.
168. *Stem the tide.* Nature, 2015. **528**(7581): p. 163-4.
169. Sato, D., Y. Arakawa, and S. Isobe, *Response to Nature's editorial regarding the Japanese legal system for regenerative medicines.* Regenerative Therapy, 2016. **4**: p. 103-104.
170. Yano, K., N. Watanabe, and M. Yamato, *Expedited approval system for regenerative medicine products – Is it unusual?* Regenerative Therapy, 2016. **4**: p. 82.
171. FDA. *Approved products: Carticel*. [cited January 2017] Available from: http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm134025.htm.
172. Mariz, S., et al., *Worldwide collaboration for orphan drug designation.* Nat Rev Drug Discov, 2016. **15**(6): p. 440-1.
173. Hayakawa, T. *Endeavour to a Minimum Consensus Package plus case by case approaches for evaluating human cell therapy products - International Regulatory Forum of Human Cell Therapy and Gene Therapy Products - Osaka, March 16, 2016*. [cited January 2017] Available from: https://www.pmda.go.jp/files/000211309.pdf.

Annex I. Approved Gene and Cell Therapy Products in the EU, US, and Japan

Table 1. Approved ATMPs in the EU

Brand name MAH	Non-proprietary name/ Product class	Submission date (S) Approval date (A) Time from filing to MA (T)	Features approval procedure	Current status in the EU / Reimbursement status	Authorization outside the EU	Description/Indication
ChondroCelect Tigenix NV	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins Tissue-engineered therapy	**S:** 01-06-2007 **A:** 05-10-2009 **T:** circa 28 months	Full approval	Withdrawn on 30-11-2016 Reimbursement achieved in 3 EU MS (Spain, Belgium, and the Netherlands)	N/A	Repair of single symptomatic cartilage defects of the femoral condyle of the knee in adults
Glybera UniQure biopharma B.B.	Alipogene tiparvovec AAV-mediated in vivo gene therapy	**S:** 23-12-2009 **A:** 25-10-2012 **T:** circa 34 months	Approval under exceptional circumstances Orphan designation Subject to additional monitoring	Available (authorized and/or commercialized only in some MS) Reimbursement not achieved	N/A	AAV-mediated in vivo gene therapy for the delivery of the human lipoprotein lipase (LPL) gene variant LPL^{S447X}. Indicated for the treatment of familial lipoprotein lipase deficiency (LPLD) with severe of multiple pancreatitis attacks in adults

MACI Vericel Denmark ApS	Matrix-applied characterised autologous cultured chondrocytes Tissue-engineered therapy	**S:** 01-09-2011 **A:** 27-06-2013 **T:** circa 23 months	Full approval Subject to additional monitoring	Suspended on 19-11-2014 Reimbursement not achieved	Authorized by US FDA on 13-12-2016	Implant consisting of patient's own cartilage cells on collagen membranes indicated for the repair of cartilage defects at the ends of the bones of the knee joint
Provenge Dendreon UK Limited	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel—T) Autologous somatic cell therapy	**S:** 30-12-2011 **A:** 6-9-2013 **T:** circa 21 months	Full approval Subject to additional monitoring	Withdrawn on 06-05-2015 Reimbursement not achieved	Authorized by US FDA on 29-04-2010	Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults
Holoclar Chiesi Farmaceutici	Ex vivo expanded autologous human corneal epithelial cells containing stem cells Tissue-engineered therapy	**S:** 06-03-2013 **A:** 17-02-2015 **T:** circa 24.5 months	Conditional approval Orphan designation Subject to additional monitoring	Available (authorized and/or commercialized only in some MS) Reimbursement not achieved	N/A	Autologous corneal epithelial cells including limbal stem cells attached on a fibrin layer for the treatment of limbal stem cell deficiency due to ocular burns in adults
Imlygic Amgen Europe B.V.	Talimogene laherparepvec Oncolytic HSV-mediated in vivo gene therapy	**S:** 28-082014 **A:** 16-12-2015 **T:** circa 16.5 months	Full approval Subject to additional monitoring	Available (authorized and/or commercialized only in some MS) Reimbursement not achieved	Authorized by US FDA on 27-10-2015	Oncolytic HSV-mediated in vivo gene therapy for the treatment of unresectable melanoma (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease in adults

Strimvelis GlaxoSmithKline Trading Service Limited	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence Ex vivo autologous hematopoietic stem cell gene therapy	**S:** 01-05-2015 **A:** 26-05-2016 **T:** circa 13 months	Full approval Orphan designation Subject to additional monitoring	Authorized only in some MS Payment by results/staggered payment model negotiated in Italy	N/A	Treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), when no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available
Zalmoxis MolMed SpA	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR)and the herpes simplex I virus thymidine kinase (HSV-TK Mut2). Allogeneic somatic cell therapy	**S:** 05-03-2014 **A:** 18-08-2016 **T:** circa 29.5 months	Conditional approval Orphan designation Subject to additional monitoring	Not yet commercialized in any country P&R procedures yet to be initiated	N/A	Adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies.

Table 2. Approved Gene and Cell Therapy Products in the US

Brand name **MAH**	**Non-proprietary name** **Product class**	**Submission date (S)** **Approval date (A)** **Time from first filing to MA (T)**	**Features approval procedure**	**Current status in the US / Reimbursement status**	**Authorization outside the US**	**Description/Indication**
Carticel Genzyme Biosurgery (current owner Vericel)	Autologous Cultured Chondrocytes	**S:** 1996 **A:** 22-08-1997 **T:** circa 12 months	PHS Act, Section 351 (Biologics) Accelerated Approval	Available Covered by insurance	N/A	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 repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft).
Provenge Dendreon Corporation	Sipuleucel-T Autologous Cellular Immuno-therapy	**S:** 21-08-2006 **A:** 29-4-2010 **T:** circa 4 years	PHS Act, Section 351 (Biologics)	Available Covered by insurance	Authorized by EMA on 6-9-2013 (withdrawn on 6-5-2015)	Autologous cellular immune-therapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.
Laviv (Azficel-T) Fibrocell Technologies, Inc	Autologous fibroblasts	**S:** 06-03-2009 **A:** 21-6-2011 **T:** circa 27 months	PHS Act, Section 351 (Biologics)	Available Reimbursement in process	N/A	Autologous fibroblasts for the improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults

Theracys Sanofi Pasteur Limited	BCG Live (Intravesical) (Bacillus-CalmetteGuerin)	**S:** **A:** 8-11-2012 **T:**	PHS Act, Section 351 (Biologics)	Available (will be discontinued in mid-2017) Covered by insurance		Attenuated live culture preparation of the Bacillus of Calmette and Guerin (BCG) strain of Mycobacterium bovis 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 tumors following transurethral resection (TUR).
Gintuit Organogenesis Incorporated	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	**S:** 13-05-2011 **A:** 09-03-2012 **T:** 10 months	PHS Act, Section 351 (Biologics)	Available Reimbursement in process		Allogeneic cellularized scaffold product indicated for topical (non-submerged application to a surgically created vascular wound bed in the treatment of mucogingival condtions in adults
Imlygic Amgen Inc.	Talimogene laherparepvec	**S:** 28-07-2014 **A:** 27-10-2015 **T:** 15 months	PHS Act, Section 351 (Biologics)	Available	Authorized by EMA on 16-12-2015	Oncolytic HSV-mediated in vivo gene therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.
MACI Vericel Corporation	Autologous Cultured Chondrocytes on a Porcine Collagene Membrane	**S:** 04-01-2016 **A:** 13-12-2016 **T**: 12 months	PHS Act, Section 351 (Biologics)	Available	Authorized by EMA on 27-06-2013	Autologous cellularized scaffold product indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults.

Table 3. Cell Therapies approved as medical devices in the US

Brand name MAH	Approval date (A)	Features approval procedure	Current status in the US	Description/Indication
Epicel Vericel Corporation	25-10-2007	Humanitarian Use Device (HUD) (unregulated device from 1988 to 1997)	Available	Cultured epidermal autografts for patients with deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%.
Apligraf Organogenesis Incorporated	22-05-1998 (for VLU) 20-06-2000 (for DFU)	Class III medical device	Available	Allogeneic bilayered tissue-engineered skin substitute composed of a dermal layer of living human keratinocytes derived from neonatal foreskin indicated for the the treatment of venous leg ulcers (VLU) and diabetic foot ulcers (DFU)
Dermagraft Advanced Tissue Sciences	28-09-2001	Class III medical device	Available	Cryoperserved human fibroblast-derived dermal substitute composed of fibroblasts, extracellular matrix and a bioabsorbable scaffold indicated for the use for the treatment of full-thickness diabetic foot ulcers greater than six weeks duration which extend through the dermis.

Table 4. Approved Regenerative Medical Products in Japan

Brand name **MAH**	**Non-proprietary name** **Product class**	**Submission date (S)** **Approval date (A)** **Time from filing to MA (T)**	**Features approval procedure**	**Current status in Japan / Reimbursement status**	**Authorization outside Japan**	**Description/ Indication**
JACE Japan Tissue Engineering Co., Ltd. (J-TEC)	Other surgical/orthopedic (autologous cultured epidermis)	**S:** 6-10-2004 **A:** 29-10-2007 **T**: circa 36 months Approved as a medical device under the previous regulatory framework	Priority review (7 years, conduct of post-marketing safety and efficacy studies)	Available Reimbursed	N/A	Autologous cultured keratinocytes derived from patient own skin tissue and cocultured with irradiated 3T3-J2 cells as a feeder to form a sheet in approximately three to seven layers thick. Indicated for use in patients with serious, extensive burns when sufficient donor sites for autologous skin graft are not available and the total area of deep dermal and full thickness burns is 30% or the total of surface area
JACC Japan Tissue Engineering Co., Ltd. (J-TEC)	Human autologous cells and tissue (autologous cultured cartilage)	**S:** 24-8-2009 **A:** 27-7-2012 **T**: circa 36 months Approved as a medical device under the previous regulatory framework		Available Reimbursed	N/A	Autologous cultured cartilage created by sampling the patient's own cartilage tissue, culturing separated cartilage cells in atelocollagens, for use by the same patient. Indicated for relief of symptoms of traumatic cartilage deficiency and osteochondritis dissecans (excluding knee osteochondritis) in the knee joints with a cartilage defect area of 4 cm^2 with no alternative therapy

TEMCELL HS Inj. JCR Pharma Co., Ltd. (licensed by Mesoblast-former Osirist)	Human (allogeneic) bone marrow-derived mesenchymal stem cell	**S:** 26-9-2014 **A:** 18-9-2015 **T:** circa 12 months	Full approval Orphan designation	Available Reimbursed	Conditionally approved in 2012 in Canada & New Zealand as Prochymal	Human allogeneic bone marrow-derived mesenchymal stem cells obtained by expanding and culturing the nucleated cells isolated from bone marrow of healthy adult donors. Indicated for the treatment of acute graft versus-host disease (acute GVHD) after allogeneic hematopoietic stem cell transplantation;
HeartSheet Terumo Corporation	Autologous Skeletal Myoblast Sheets	**S:**30-10-2014 **A:** 26-9-2015 **T:** circa 11 months	Conditional/Time-limited approval (5 years, conduct of post-marketing efficacy studies)	Available Reimbursed	N/A	Human autologous skeletal myoblast-derived cells consisting of the patient's skeletal myoblasts that have been cultured, proliferated and cryopreserved as the main component, and the instruments etc. for shaping the cell sheets in medical institutions as sub-components. Indicated for the treatment of serious heart failure caused by ischemic heart disease by applying the sheet-shaped cells to the surface of the heart during the open chest surgery then standard therapies are not sufficiently effective.

Annex I Sources:

Europe

EMA. European public assessment reports**.**

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125

Abou-El-Enein et al. Overcoming challenges facing advanced therapies in the EU market. Cell Stem Cell. 2016. 19:293.

Dellamano, R. et al. ISPOR 19th Annual European Congress. Vienna, Austria October, 2016. Advanced Therapy Medicinal products (ATMP) in Europe 8 years on: what is the path to market access so far? https://www.ispor.org/research_pdfs/54/pdffiles/PHP222.pdf

United States

FDA. Cellular & Gene Therapy Products: Marketed Products.

http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/default.htm

EC. Study on the regulation of advanced therapies in selected jurisdictions

Dodson and Levine. Challenges in the translation and commercialization of cell therapies. BMC biotechnology. 2015 15:70.

FDA. Device Approvals, Denials, and Clearance.

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/default.htm

Japan

PMDA. Medical Devices. List of approved products. https://www.pmda.go.jp/english/review-services/reviews/approved-information/devices/0001.html

J-TEC. Press release: J-TEC received government approval to manufacture and sell autologous cultured cartilage JACC in Japan.

http://www.jpte.co.jp/english/ir/library/JACC_20120730E.pdf

Yano, K et al. Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan. Regenerative Therapy 1 (2015) 45-56.

PMDA. FY 2015 New Regenerative Medical Products. https://www.pmda.go.jp/files/000214524.pdf

PMDA. Review Reports: Regenerative Medicines. https://www.pmda.go.jp/english/review-services/reviews/approved-information/0004.html

Annex II – Japanese system of pharmaceutical law and regulatory documents for regenerative medicine

Table 1 – Japanese system of pharmaceutical law

<table>
<tr><td>1. Pharmaceutical & Medical Device Act (PMD Act)</td><td>Based on Parliamentary Resolution (Law)</td><td rowspan="3">Having legal force:
e.g. compelling power about penal regulations (suspension of business, penal charge etc.)</td></tr>
<tr><td>2. Cabinet Ordinance</td><td>Issued by Cabinet</td></tr>
<tr><td>3. Ministerial Ordinance and Ministerial Notification</td><td>Issued by minister of MHLW</td></tr>
<tr><td rowspan="3">4. Notification</td><td>Issued by head of Bureau
(e.g. Pharmaceutical Food Safety Bureau - PFSB)</td><td rowspan="3">Administrative direction:
detailed explanations or operation statements about Laws. Violation can lead to the formal letter of apology signed by head of business</td></tr>
<tr><td>Issued by head of Division
(e.g. Evaluation and Licensing Division -ELD)</td></tr>
<tr><td>Issued by Division</td></tr>
</table>

Adapted from Fiedler, B. MDRA16. Module 3. International Registration Procedures: Japan.

Table 2 – Overview of important regulations and guidance documents for regenerative medicine products under the PMD act and regenerative medicine under the ASRM

Regenerative Medicine Products under the PMD Act	
Name of regulations or guidance documents	*Official number of act, cabinet ordinance (CO), MHLW Ministerial ordinance (MO), MHLW Minister's notification (MN) and related guidance*
<u>Regulations</u>	
Pharmaceuticals and Medicals Devices Act	1960 Act No. 145 revised by 2013 Act No. 84 (November 27, 2013)
Revised CO for the enforcement of the PMD Act	1961 CO No. 11 revised by 2014 CO No. 269 (July 31, 2014)
Revised CO for user fees related to the PMD Act	2005 CO No. 91 Revised by 2014 CO No. 269 (July 31, 2014)
Revised MO for the enforcement of the PMD Act	1961 MO No. 1 revised by 2014 MO No. 87 (July 31,2014) and PFSB Director Notice 0806 No. 3 (August 6,2014)
Revised MO for user fees related to the PMD Act	2000 MO No. 63 revised by 2014 MO No. 87 (July) 31, 2014) and PFSB Director Notice 0812 No. 35 (August 12,2014)
Name of regulations or guidance documents	*Official number of act, cabinet ordinance (CO), MHLW Ministerial ordinance (MO), MHLW Minister's notification (MN) and related guidance*
Good clinical practice (GCP)	2014 MO No. 89 (July 31,2014), PFSB Director Notice 0812 No. 16 (August 12, 2014), and MRED Director Notice 1121 No. 3 (November 21, 2014)

Good post-market study practice (GPSP)	2014 MO No. 90 (July 31, 2014), PFSB Director Notice 0812 No. 23 (August 12,2014), and MRED Director Notice 1121 No. 7 (November 21, 2014)
Good gene, cellular, and tissue-based products manufacturing practice (GCTP)	2014 MO No. 93 (August 6, 2014), PFSB Director Notice 0812 No. 11 (August 12, 2014), and Compliance Division Director Notice 1009 No. 4 (October 9, 2014)
Good quality practice (GQP)	2004 MO No. 136 revised by 2014 MO No. 87 (July 31, 2014) and PFSB Director Notice 0812 No. 11 (August 12, 2014)
Regulations for buildings and facilities	1961 MO No. 2 revised by 2014 MO No. 87 (July) 31, 2014) and PFSB Director Notice p812 No 11 (august 12, 2014)
Good vigilance practice (GVP)	2004 MO No. 135 revised by 2014 MO No. 87 (July 31, 2014) and PFSB Director Notice 0812 No. 1 (August 12, 2014)
Standards for biological ingredients	2003 MN No. 210 revised by 2014 MN No. 375 (September 26, 2014) and PFSB Director Notice 1002 No. 27 (October 2, 2014)
Major administrative guidance documents	
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 authorization	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)
Guidance on GCTP/GQP/regulation 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 infection disease surveillance reports	PFSB Director Notice 0812 No. 7 (August 12, 2014) and Safety Division Director Notice 1113 No. 4 (November 13, 2014)
Guidance documents related to product quality, safety and efficacy (subgroup- or product-specific guidelines)	
Guidance on standards for biological ingredients	ELD Director Notice 1002 No. 1 and MRED Director Notice 1002 No.5 (October 2, 2014)
General principles for the handling and use of cells/tissue-based products	Pharmaceutical and Medical Safety Bureau Director Notice No. 1314 Appendix 1 (December 26, 2000)
Guideline on ensuring the quality safety of products derived from processed:	
Autologous human cells/tissues	PFSB Director Notice 0208 No. 3 (February 8, 2008)
Allogeneic human cells/tissues	PFSB Director Notice 0912 No. 6 (September 12, 008)
Human embryonic stem cells	PFSB Director Notice 0907 No. 1 (September 7, 2012)
Autologous human somatic stem cells	PFSB Director Notice 0907 No. 2 (September 7, 2012)
Allogeneic human somatic stem cells	PFSB Director Notice 0907 No. 3 (September 7, 2012)
Autologous human induced pluripotent stem(-like) cells	PFSB Director Notice 0907 No. 4 (September 7, 2012)
Allogeneic human induced pluripotent stem(-like) cells	PFSB Director Notice 0907 No. 5 (September 7, 2012)
Name of regulations or guidance documents	*Official number of act, cabinet ordinance (CO), MHLW Ministerial ordinance (MO), MHLW Minister's notification (MN) and related guidance*
Points to consider for the evaluation of specific products	
Cell sheet for heart failure	OMDE Director Notice 0118 No. 1 (January 18, 2010)
Corneal epithelial cell sheet	OMDE Director Notice 0118 No. 1 (January 18, 2010)
Corneal endothelial cell sheet	OMDE Director Notice 0528 No. 1 (May 28, 2010)
Articular cartilage repair	OMDE Director Notice 1215 No. 1 (December 15, 2010)

Cell sheet for periodontal tissue regeneration	OMDE Director Notice 1207 No. 1 (December 7, 2011)
Autologous iPS cell-derived retinal pigment epithelial cells	OMDE Director Notice 0529 No. 1 (May 29, 2013)
Allogeneic iPS cell-derived retinal pigment epithelial cells	OMDE Director Notice 0912 No. 2 (September 12, 2014)
Regenerative Medicine under the Act on the Safety of Regenerative medicines (ASRM)	
Name of regulations or guidance documents	*Official number of act, cabinet ordinance (CO), MHLW Ministerial ordinance (MO), MHLW Minister's notification (MN) and related guidance*
Regulations	
Act on the Safety of Regenerative Medicine (ASRM)	2013 Act No. 85 (November 27, 2013)
CO for the enforcement of the ASRM	2014 CO No. 278 (August 8, 2014)
CO for the enforcement of the ASRM	2014 MO No. 110 (September 26, 2014)
Guidelines for human stem cell therapy clinical research	2006 MN No. 425 (July 3, 2006) 2010 MN No. 380 2013 MN No. 317
Guidance documents	
Related to Operation of Guideline for human stem cell therapy clinical research	Health Service Bureau Notification No. 0703003 (July 3, 2006)
Processes for human stem cell therapy clinical research	Report for HSC. MHLW (May 18, 2006)
Processes for evaluation of human stem cell therapy clinical research based on "Guideline for human stem cell therapy clinical research"	Report for HSC. MHLW (July 27, 2006)
Q&A on "Guideline for human stem cell therapy clinical research"	Specific Disease Control Division Document

Adapted from Azuma, K. Regulatory Landscape of Regenerative Medicine in Japan. Curr Stem Cell rep (2015) and Maeda, D. et al. Regulatory Frameworks for Gene and Cell Therapies in Japan. Springer International Publishing (2015).

Annex III. Overview of the regulation of advanced therapies in the ICH jurisdictions

	Europe	United States	Japan
Legal basis for regulation of gene and cell therapy products	- Regulation 1394/2007 - Directive 2001/83/EC (amended by implementing Directive 2009/120/EC) - Directive 2004/23/EC and implementing directives - Directive 20012/98/EC and implementing directives	- FD&C Act - PHS Act Section 351 (biologics review) - Title 21 CFR: - Biologics: 21 CFR 600-680 - Devices: 21 CFR 820-899 - HCT/Ps: 21 CFR 1271	- Revised Pharmaceutical Affairs Law (PMD Act) - Cabinet and ministerial ordinances for enforcement of the PMD Act - Ministerial notifications
Regulatory oversight	- EC/EMA for marketing authorisation - National authorities for: - clinical trial approval and supervision - sourcing of cells and tissues - material of biological origins - GMO - Hospital Exemption and Compassionate Use Programs	- FDA	- MHLW/PMDA
GMP, GCP requirements	- GMP for entire development, including early phases (Directive 2003/94/EC) - ICH-GCP	- CGMP (21 CFR 210-211) Flexibility in Phase I CT (GCMP for Phase I investigational drugs) - ICH-GCP	- GCTP for marketed products - 'GMP for investigational products' during CT - ICH-GCP (local implementation) - J-GCP

	Europe	United States	Japan
Early access schemes	- Conditional MA - MA under exceptional circumstances - Adaptive pathways - Accelerated assessment - PRIME	- Accelerated approval for serious or life-threatening diseases - Priority review - Break through therapy - Fast track designation (with rolling submission and review)	- Conditional & time-limited approval for regenerative medicine - Priority review - Sakigake designation (prioritised consultations and review, rolling submission and review)

Other support for developers	- Scientific advice
	- EMA-HTA parallel scientific advice
	- EMA-FDA parallel scientific advice
	- Orphan designation:
	  - Protocol assistance
	  - Eligibility for accelerated review
	  - Tax credits (Member State specific)
	  - Research grants (Member State specific)
	  - Reduced registration fees
	  10 years market exclusivity
		- Scientific advice
		- EMA-FDA parallel scientific advice
		- Orphan designation:
		  - Protocol assistance
		  - Priority review
		  - Tax credits (up to 50% of clinical research cost)
		  - Annual grant funding for clinical studies
		  - Exemption from registration fees
		  - 7 years market exclusivity
		- Rare paediatric Disease Priority Review Voucher
			- Scientific advice
			- Orphan designation:
			  - Protocol assistance
			  - Priority review
			  - Tax credits (6 % of clinical and nonclinical studies)
			  - Research grants for clinical and nonclinical studies
			  - Extension of the post-approval reassessment period
			  - 10 years market exclusivity

	Europe	United States	Japan

Alternative access routes (other than participation in CT and treatment with authorized products)	- Hospital Exemption (regulated at national level)
	- Compassionate use programs (regulated at national level)
		- Expanded access programs:
		  - For individual patients
		  - For intermediate-size patient population
		  - For wide spread use
			- Clinical research and medical practice under the ASRM
			- Off-label use under the ASRM
			- Compassionate use program under the PMD Act
			- Patient-Proposed Healthcare Services (PPHS)

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Köln, 25.02.2017

Dr. Valeria Facchinetti