TÉCNICO LISBOA

Value creation in the cell therapy industry

The role of regulation

Tânia Rafaela Nunes Agostinho

Thesis to obtain the Master of Science Degree in

Biomedical Engineering

Supervisors: Dr. Joana Serra da Luz Mendonça

Dr. Daniela Andreia dos Santos Couto

Examination Committee

Chairperson: Prof. Luís Humberto Viseu Melo

Supervisor: Dr. Joana Serra da Luz Mendonça

Members of the Committee: Prof. Frederico Castelo Alves Ferreira

November 2016

Acknowledgments

My sincere gratitude for the help and support of who in way or another have contributed to the development of my master thesis

- To Joana Mendonça, my coordinator, who I am very thankful for the patience, guidance, encouragement and constructive opinions.
- To Miguel Amador and Miguel Forte and Daniela Couto for their patience, willingness to help and valuable suggestions during the project and without whom some of the established contacts will be never possible.
- To Eduardo Bravo, Margarida Menezes, Claudia Lobato da Silva and Robert Deans who had dispensed of their valuable time to participate in the interviews process and enriched my thesis with their experiences.
- To my family and best friends who inspired me through all the project.

Abstract

The cell therapy industry is a recent industry presenting great potential for cure of a variety of diseases, some of them associated with high healthcare expenses[1,2]. This disruptive technology is associated with a set of requirements and challenges that need to be overcome in order to allow the industry to achieve its maximum potential and meet the expectations[3,4].

The main goal of this study is to collect and analyse opinions related to the constraints, limitations and impacts of regulation currently faced. During this investigation an interview protocol was established in order to collect information from various stakeholders of the industry.

The results obtained in the investigation were systematized and presented through the use of conceptual maps and summary tables in order to facilitate the exposition and discussion of the findings. The relations of influences across the objects of study and the comparison between the opinions of the experts according each field were specified.

The points of view of the interviewed, about the issues responsible for hindering the cell therapy Industry from its maximum potential don't show large disparities. The markets vary according the different geographical regions and one of the reasons for this phenomenon is the different legislation applied. Inexperience, funding and regulation are currently impacting the creation of value, being associated with multiple barriers and obstacles to the sector's growth. The commercialization of products through the Hospital exemption scheme has negative impacts in the commercialization of other cell based products and in the competition between both types of products.

Keywords: Cell therapy; Regenerative medicine; Hospital exemption; Value creation; Regulation.

Resumo

A indústria de terapias celulares é recente e apresenta elevado potencial de cura para uma grande variedade de patologias associados a elevados custos em saúde[1,2]. Esta tecnologia disruptiva está relacionada com um conjunto de requisitos e desafios que devem ser superados para que seja possível atingir o seu máximo potencial e corresponder às expectativas que a rodeiam[3,4].

Durante este estudo foi desenvolvido um protocolo de entrevistas com o objetivo de recolher informações acerca dos constrangimentos, obstáculos e limitações encontrados durante o desenvolvimento e comercialização de terapias celulares. As opiniões acerca da existência de Isenções hospitalares e da competição dos produtos desenvolvidos através desta via com os restantes produtos foram analisados.

Os resultados obtidos ao longo da investigação realizada foram sistematizados e apresentados através de mapas conceptuais e tabelas de resumo de modo a facilitar a exposição e discussão dos resultados. As relações de influência presentes entre os diversos objetos do estudo e a comparação de opiniões são explícitos ao longo da apresentação de resultados.

Os pontos de vistas recolhidos entre os participantes, acerca dos aspetos responsáveis por restringirem a indústria de atingir o seu máximo potencial não apresentam grandes disparidades. As desigualdades na legislação em vigor nas diferentes localizações geográficas são um dos principais motivos apresentados para a existência de diferenças nos mercados. A Inexperiência, investimento, regulação impactam atualmente a criação de valor. A comercialização de produtos desenvolvidos através de isenções hospitalares apresenta um impacto negativo nestes mercados, constituindo uma oportunidade para a ocorrência de competição.

Palavras-Chave: Terapias celulares; Medicina Regenerativa; Hospital exemption; Criação de valor; Regulação.

Contents

List of Figures

List of Tables

1. Introduction

Cell therapy industry already captured attention from patients, doctors and academia due its potential. Despite all the investments made in research in this area, and the increase in sales volume and markets growth, there are several examples of cell therapies approved by major regulatory agencies that didn't achieved success when in market[5].

This investigation aims to study the challenges and hurdles associated with the development of the cell therapy industry in general and address some of the issues that have hindered this industry from reaching its full potential. The technologic platforms and the establishment of value chains for cell therapies and the associated hurdles are also object of study, as well as the impact of regulatory frameworks in the creation and establishment of value chains in this industry.

The existence of regulatory exceptions such as hospital exemption in the existent legislation for advanced therapy medicinal products in which cell therapies are included will be addressed in this investigation. The impact of therapies from hospital exemption in the cell therapy market, namely in therapies already approved and in therapies in development for the same diseases will also be investigated. The major goals of this work are the development of an extensive analysis of the main problems related to the creation of value in this specific industry and the development of possible recommendations based in the bibliographic review and in experts' opinions collected during the research.

In order to address these issues, a set of research questions was defined:

- *"Which are the major hurdles for the establishment of value chains for cell therapies?"*

Despite all the potential already demonstrated by the Regenerative Medicine and recognized by the academy, patients and medical doctors, the development, commercialization and application of such therapies are still below their maximum potential, which may only be achieved, overcoming some obstacles[6]. The identification of these obstacles for different stages of development of a new therapy is one of the objectives of this study. Opinions of scientific developers, doctors and regulators will be taken into consideration. The aim of the study is not only to evaluate the main obstacles during the development and commercialization of new therapies, but also is to identify the hurdles that prevent their success even when they achieve the markets.

- *What is the impact of regulatory exceptions (namely, Hospital exemption) in the creation and establishment of value chains for approved regularly cell therapies?" And "What is the impact of Hospital exemptions in the Cell therapy market (approved products)"?*

There are several pathways for the development of cellular therapies and subsequent commercialization. The current directives from the European Medicines Agency allow the existence

of the hospital exemption scheme[7], which is a mean for patients to access a customized advanced therapy medicinal product, category in which cell therapies are included, under specific circumstances.

One of the goals of this work is to study if the products originated from hospital exemption affect the value chains of products approved by regular pathways, and how they do that, namely if they affect the relation of the companies with the suppliers, final clients and all the other intervenient during the production and marketing phases.

- *"Could the therapies arising from the hospital exemption scheme be considered as having competitive advantages"?*

The differences in regulation and requirements for the development and commercialization of new cell therapies when they follow hospital exemption pathway/ route/ scheme, lead to different opportunities for these products in the entrance in the market[8,9]. Throughout this study, one of the goals is to collect views and experiences of stakeholders linked to cell therapies developed outside of the exemption route, which are currently competing with cell therapies developed through the hospital exemption scheme, trying to better understand the competition between the two types of products and to find examples that may illustrate the results of the competition between these products.

- *"Are there differences between USA and EU legislation concerning cell based therapies?"*

Concerning legislation, and although the current efforts made by the regulatory agencies, to homogenize the guidelines between the different member states from all around the world there are still some differences in legislation causing an impact in the development and commercialization of new therapies[10]. These study aims to understand how the stakeholders deal with these dissimilarities, and the implications of their impact. The focus will be the organizational differences between the United States of America and European Union, Food and Drug Administration (FDA) and European medicines agency (EMA) respectively.

The study presented hereinafter intend to be an exploratory analysis of the study subjects previously presented. In order to achieve our goals a literature review was performed, being our main focus the regulatory environment which regulates the cell therapy industry, the regulatory exceptions allowed and the conditions that lead to a successful commercialization of new cell-based products. A set of interviews to stakeholders directly related with the commercialization of new cell therapies, regulators and academics were also performed with the aim of collect points of view from different industry sectors and understand if they diverge or converge concerning the sector of the players. The results from the interviews are present and systematized in summary tables and conceptual maps.

1.1. Study Overview

To facilitate the readings and understanding of this study, this thesis is divided into 7 major Chapters: The present chapter presents the motivation for choosing this theme and provides a framework for the proposed study. In Chapter 2 the methodological approaches used are defined and explained. In Chapter 3 we provide an overview of the context of the cell therapy industries as well as its characterization, namely a presentation of its main drivers and investors and a description of its market evolution through the last years as well as forecasts for the coming years. Chapter 3 contains also an analysis of the importance of the early definition of a market access strategy, including the main keys considered to be by the stakeholders, responsible the successful commercialization of a new cell therapy product. A data collection of the emerging business models and their differences depending on the product characterization are also present, as well as an analysis of the importance of pricing and reimbursement definition. Value chains, supply chains and logistic processes associated with the creation of value for the cell therapy industry are also object of analyses of the Chapter 3.

In Chapter 4 the regulatory environment that supports this industry is presented. The regulatory framework of the cell therapy industry in Europe is explained, the definition and explanation of an advanced therapy medicinal product is also in this chapter, as well as the analyses of the approval process of a new cell therapy and the documents required. The presentation of the regulatory exceptions allowed by current regulatory environment responsible for enable a quicker route to market to some cell based products is also present in this chapter. *Hospital exemption* definition and creation motifs, current feedback and critics from stakeholders and the direct comparison with other regulatory exception, "*les specials"* are topics covered in this chapter.

Chapter 5 includes the presentation of the results of the interviews to the stakeholders from the different sectors and the presentation of a case study about *ChondroCelect,* a cell therapy developed by *Tigenix*. Lastly, Chapter 6 contains the main conclusions of this study and Chapter 7 contains the references and sources consulted during the investigation

2. Methodology

In this chapter will be presented the main approaches chosen to collect, systematize and present the findings about the subject presented in the previous chapter. A brief description of the interviews performed in the course of this investigation as research tools and the reasons for its use could be consulted in the next sections, as well as the justification of the use of a case study approach and the data analysis strategies selected

2.1. Interviews

Interviews are a method of research that allows the collection of data with detail without losing the experiences, perspectives and views of respondents and without limiting responses and opinion[11] relevant characteristics that led to the selection of this methodology.

With the aim of obtain the desired information to be analyzed during the project a set of questions was prepared to be performed to players in the industry of cell therapies industry from different areas. Taking into account that the interviews would be performed to participants who have different backgrounds the type of interview selected was semi-structured, technique that makes possible the standardization of some questions and the replication of the process but also allows the possibility of asking spontaneous questions depending on the participant previous responses.

The set of questions established to function as interview guidelines for the semi-structured interview to be performed to the cell therapy industry players covers the various topics which are intended to be studied. The questions focus the hurdles associated with commercialization of cell therapy products, the establishment of the value chains and the impact hospital exemption products. In the Supplementary Data section is possible to consult the interview protocol used during the study.

2.2. Case study

We used a qualitative case study approach to focus on one product which are already in the market allowing us to describe a real example of development and commercialization of a cell therapy product and the main processes and challenges associated. The reasons that lead us to choose this approach are mainly related to the fact that this methodology offers the chance to perform an investigation about complex environments becoming an important method to develop theories and evaluate the need of interventions using multiple resource sources[12].

The first step of this approach was the definition of 4 research questions, which were the basis for the study and are presented and justified in chapter 1. The definition of the research questions were followed by the choice of the type of the cases study desired. According to the objectives of

the study it was concluded that the best option would be a descriptive case study, once type of case approach is used to describe an intervention or phenomenon and the real-life context in which it occurred[13].

2.3. Data collection and analysis

Aiming the triangulation and consequent validation of the data present in this study, a combination of qualitative and quantitative information was collected from multiple data sources during the development of this project. Interviews performed were one of the most important sources, as well data collected through a literature review. Reports, directives, legislation and other documents were also used.

Given the open-ended nature of the questions performed during the interviews, one of the qualitative data analyses strategies used in this study are conceptual maps, this approach is used to present some of the main ideas of collected during the interviews. This methodology was selected since it allows to display links between ideas allowing a schematic organization and presentation of the data, being one of the main advantages of this methodology the visual representation allowed and ease of use. The fact that this type of approaches allow the reduction of data maintaining the meaning of the answers and the representation of the interconnections in the study was other advantage considered[14]. The conceptual maps developed in this study were created according to the guidelines proposed in the article *Mapping methods for qualitative data structuring by Jenny Bringhtman* [15]

3. Cell therapy industry

The information contained in the next sections are the result of a literature review performed as an exploratory analyses to collect information about of the current state of the cell therapy industry, the evolution of this sector, the influencers of this market and major handicaps of this field. The information presented in this chapter aims to provide the reader a broad contextualization about the cell therapy industry useful for the discussion of the following chapters.

Currently the population is progressively more affected by degenerative diseases caused by aging and unhealthy lifestyles. Drugs and surgeries are the most common used tools to diminish the symptoms of these conditions, until know, but are many times associated with the mitigation of symptoms and not with the real cure[16].

The concept of cell therapy refers to the administration of live cells to a patient aiming the treatment of a disease through the repair or regeneration of defective functions of a damaged tissue, presenting new hopes in the cure or treatment of previously incurable diseases[2,17]. Along with medical devices, artificial organs, tissue engineering and biomaterials, cell therapy is integrated in the field of regenerative medicine[18]. The economic return from regenerative medicine is expected to be of over orders of magnitude from tens of millions to billions of dollars and the employment is expected to be from tens of thousands to hundreds of thousands of jobs, where, healthcare systems, aiming to provide sustainable and comprehensive healthcare for the population will be the major markets for these type of therapies[19].

Despite the research related to the development of cell-based therapies have little over 50 years, cell therapy industry has shown a favorable market growth and increasing attention from patients, academia and medical community in the recent years. The cell therapy market is still immature but this industry is already considered the fourth pillar of global healthcare, together with the pharmaceutical Industry, the medical devices industry and biotech[4].

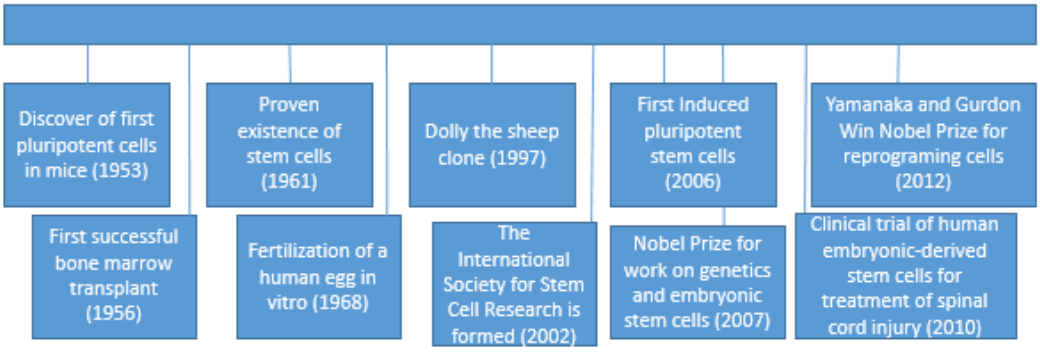

Figure 1 Major milestones in the development of the cell therapy industry

In Figure 1 is possible to find the major milestones in the cell therapy industry since the discover of the first pluripotent cells in mice until 2012, the date related to the winning of the Nobel prize for reprograming cells[20,21]. There are already available on the market cell therapies constituted by cells of different types, from different sources and to be applied several different clinical conditions. At the present, therapies including embryonic stem cells and induced pluripotent stem cells are still in the begging of the process of clinical development once, due their nature, these cells are still associated with ethical and safety issues. Despite the diversity of existing therapies and therapies in development, it is possible to structure the cell therapy industry in two major sections, autologous cell-based products and allogeneic cell based products[22].

Currently, there is volatility associated with the cell therapy industry caused by several factors. This volatility is derived to causes common to all the emerging technologies, which have often some initial volatility followed by periods of stability and greater growth. The current global economic crises is other driver of volatility, cause currently common to global financial markets which are affected by uncertainty. At last, the causes unique to the cell therapy industry which are the disruptive nature of the technology that makes challenging to predict its impact and the fact that many of the organizations of the industry are interdependent to variable degrees. The minimization of volatility is necessary in order to improve confidence and increase investments[23].

Being a technology with a disruptive nature[3], cell therapies are associated with some requirements related with the scientific breakthrough and with the infrastructures needed to allow commercialization of new therapies and services. The development of knowledge in the field, new infrastructures and funding are required, as well as appropriate regulation. New business models as well as other logistic processes are also desired once the existent ones, used by the pharmaceutical industry does not fit correctly the nature and requirements of the cell therapy processes[24].

3.1. Main Drivers and Investors

The main drivers for innovation in this area are the existent unmet medical needs, the possibility of personalized medicine and the progresses and results already achieved through years of research and clinical studies[3]. Currently, cell therapy has the potential to allow a reduction in healthcare expenditures, offers a higher quality of life for patients and has the potential to provide potential cures instead of only small improvements being these some of the main reasons to invest in this field[2]

In 2007 a study showed that the joined costs of the seven most common chronic diseases in the United States were about $1.3 trillion annually[1]. Chronic diseases are commonly associated with

high co-morbidity costs and complications, being the most economically burdensome diseases. Only in United States the potential savings in healthcare expenditure due to regenerative medicine, in which are included cell therapies, are expected to be about $250 billion per year[2].It is therefore expected that the cure, or reduction of this complications due to cellular therapies, allow a significant decreasing in healthcare expenditures, making this, one of the Cell therapies main targets.

The pharmaceutical industry, the medical devices industry and biotech industry have already demonstrated interest in investing in this field. Although there are investments from the pharmaceutical industry in this area, specifically from big pharmaceuticals like Pfizer, Novartis and Astellas Pharma, who already invested in the development of cell based therapies, it is possible to verify some reluctance in investing[25]. The great investments required, the complexity associated to the product development, the concerns with efficacy, safety and regulation and the inexperience associated to the commercialization of these solutions have been limiting factors to the evolvement of pharmaceutical industry[17,26]. It is also important to highlight that the interest of the big pharma's industry in concentrated in products for broad-based use, as allogeneic cell therapies[19].

Funding for cell therapies development comes from different sources, private and public organizations are nowadays interested in investing in this field attracted by the market growth. Disease organizations, biotechnology companies and pharmaceuticals had made investments. However there are still some barriers for the investment in this field. Long development cycle timescales associated to these type of solutions could be unattractive for the investors, also, the complexity of cell based therapies, the absence of developed and proved business models and the hurdles evolving the regulatory systems could be considered funding barriers[19].

In Europe, data from the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database shows that from the main sponsors for the development of 318 ATMP trials (between 2004 and 2010) were academia, charities and other small companies[27]. The data illustrated in Figure 2, allow us to understand the distribution of the main funders by percentage and by phase of research. It is possible to observe that academia and hospitals are the main funders in every stages of the development of a new therapy. It is also possible to conclude that Industry, is the smaller funder in every stages of the process, being even in some cases absent in phases 1 & 2, existing a very low representation of Industry (private funds) when comparing with other sponsors, namely, academia, hospitals and National Institutes of Health (NIH)[3].

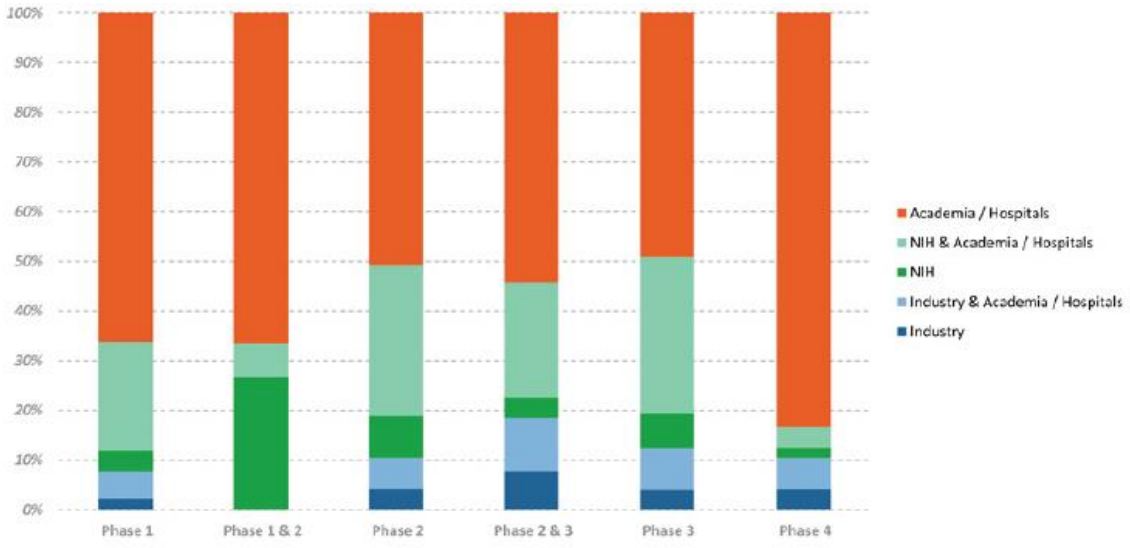

Figure 2 Main Funders by Research and Development phases in the cell therapy industry. (Source: European biopharmaceutical Enterprises & Transformation 2015[3]*)*

3.2. Market Evolution

Until now, more than 10 cell therapy products were approved by FDA and EMA, and there are more than 40 cell therapy products available on the market, for several conditions, including, prostate cancer (Provenge) and cartilage defects of the femoral condyle (ChondroCelect)[28–30].

In Figure 3 is possible to observe a list of approved gene and cell therapy products in Canada, United States, Europe, Japan, South Korea and China. We can observe by these data that there are currently, no common therapies around the world, which is caused due to different regulations and requirements established by local regulators that prevent the use or commercialization of some therapies in some countries although they are approved in other[31].

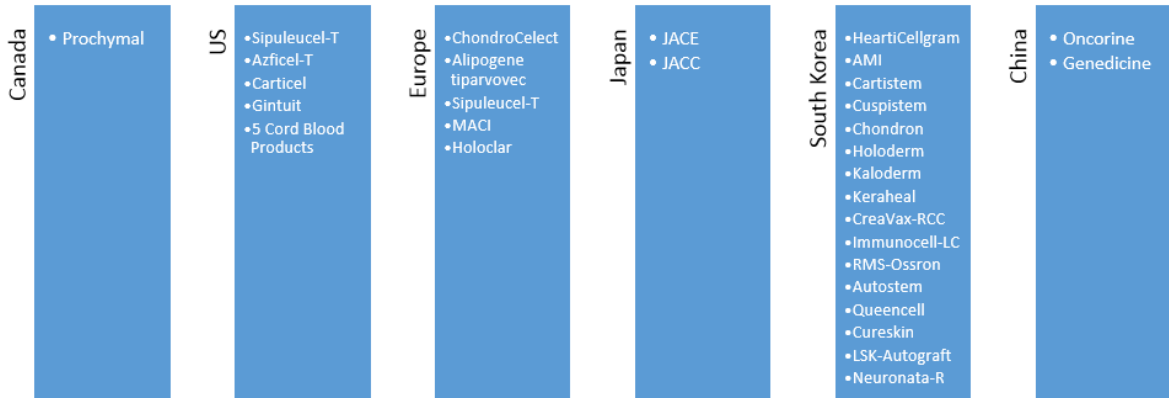

Figure 3 Approved gene and cell therapy products in Canada, US, EU, Japan, South Korea and China[22]

By January 2014, there were 1342 active clinical trials (in clinicaltrials.gov), in which hematopoietic cells, mesenchymal stem Cells, lymphocytes and dendritic cells are the most common types of cells in the represented studies[22]. Expectations around cell therapies are increasing, due to the positive results of products already on the market and to promising results of products in development. Currently, in the European markets the main customer of cell therapies is the state, while in the United States the private sector is the main healthcare buyer[32].

This type of solutions has been considered as having great potential for application in a wide range of conditions. Oncology is the biggest target for cell therapies in clinical trials[22], chronic diseases, major trauma, neuro-degenerative, musculoskeletal and cardiac disorders are the other key targets for the treatments currently in development[4,33]. The enthusiasm around these therapies is considered recent but the research on this field is not, experiments considering the administration of stem cells in bone marrow transplantation have been used since 1968, human cells have been used mainly in transfusion field and in hematological conditions[22,25].

Although it is considered a recent business, cell therapy industries had already lucrative results. In 2010 the 20 cell therapies most sold produced revenues of about $460 million[30].Progressing from market values of a few million dollars to $2.7 billion in 2011, with the current developments in the field and with new approved products, the cell therapy market is expected to progress to $8.8 billion by 2016[25]. It is also expected an expansion of the market to $20 billion worldwide by 2025[34].

In the period between 2015 and 2020 is predictable that the growth will occur at a higher compound annual growth rate in emerging countries emerging countries than in developed countries and the estimated compound annual growth rate is also superior in allogeneic cell therapy market then in the autologous cell therapy. Despite all the promises the clinical availability of cell therapies continues to be challenged and in order for the market to achieve is full potential it is necessary to overcome several hurdles, which are currently responsible for restraining its growth, namely, ethical issues, lake of infrastructures and problems related to storage and transportation of therapies. Costs, scalability of the production processes and regulatory hurdles are also obstacles, as well as lack of proven business and investment models[6].

In Figure 4 it is possible to observe the estimated Cell therapy Industry Revenues from 2008 to 2014, the evolution of the revenues related with cord blood banking and with the total stem cell market[4].

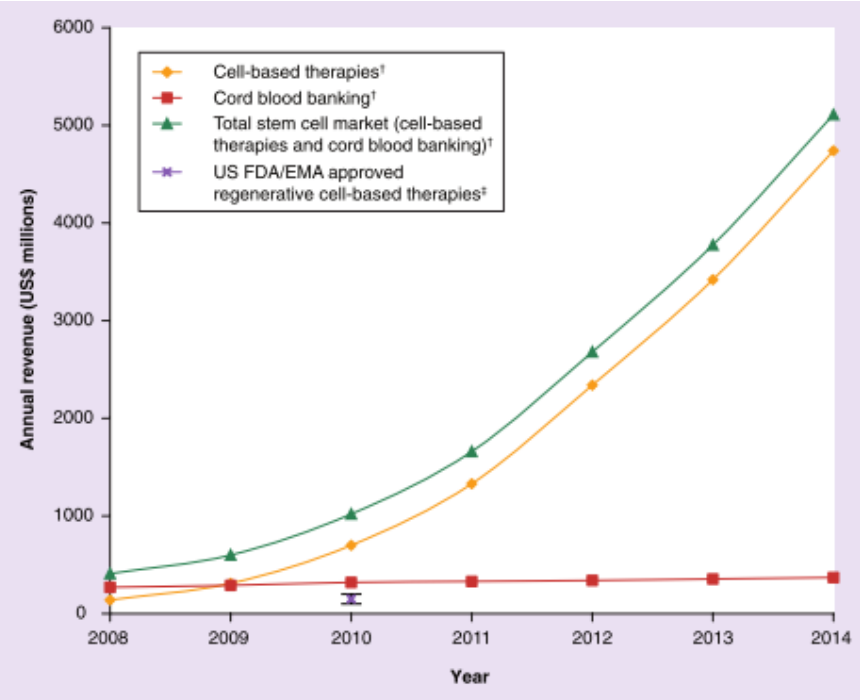

Figure 4 Cell therapy industry market (2008–2014) (Source: Mason et al. 2011)[4]

3.3. Translation and Innovation

The translation of a technology and the Innovation are key processes in the development and creation of value for new therapy products. Both processes are complex and crucial for the progress and expansion of the cell therapy industry, consequently existing limitations in these areas could prevent the success of new discoveries and their commercial success.

3.3.1. Translational Process and Gaps

The translation of a technology is not linear. This process allows a scientific breakthrough (for example cell therapy products) to gain value and to become commercially viable products through a set of activities such as development, implementation and integration by the industry. This process requires an extensive collaboration between industry stakeholders, including scientists, clinicians and managers in order to provide feedback information between them and generate continuously new hypothesis, allowing the cycle to evolve and introduce new findings into practice[32,35].

There are two core translational gaps already identified in the process, the "Translational Gap 1" or "Valley of Death" and the "Translational Gap 2". The translation gap 1 is related to the difficulties

arising from clinical trials, regulation problems and funding, and occurs between the preclinical development and the end of the clinical phase II. The second gap arises from human behavior and is related to organization, infrastructures, and reimbursements, and occurs after the end of the clinical phase III to the end of the knowledge management phase[35].

To increase the number of products with commercial potential reaching the markets, these translation gaps should be "bridged", which would require an effort by multiple entities. In Figure 5 is possible to observe a schematic representation of the main milestones and the critical path covered during the development and introduction in market of a new cell therapy, it also allows to contextualize the existing translation gaps in the general process[35].

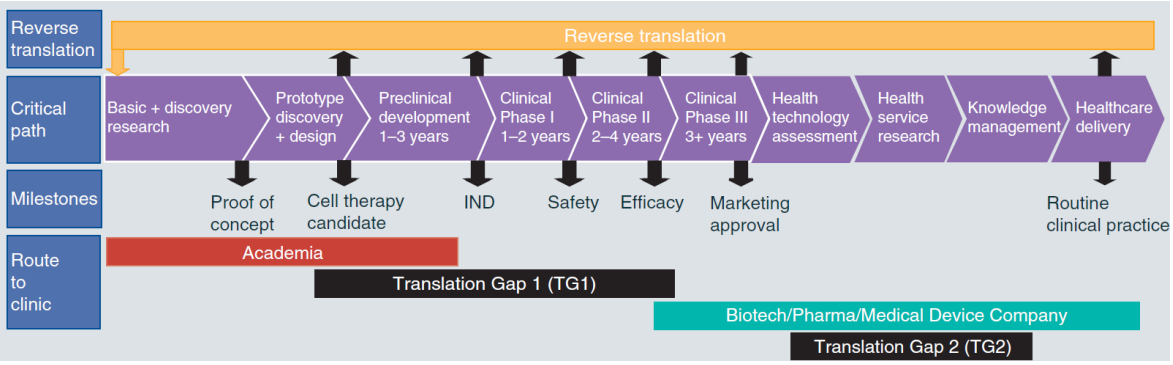

Figure 5 Translation Cycle for cell-based therapies. (source: Mason & Manzotti 2010[35])

3.3.2. Innovation models

A study performed in the scope of the project "State strategies of governance in global biomedical innovation" developed by the Department of political economy of King's college London, grouped the main stem cell innovation models applied in the production of stem cell therapies. We are using the results of the project to frame our analysis.

The Scientific Innovation model presented in Figure 6, requires five stages until the product reaches the market: Basic Research; Clinical Experimentation; Product Development; Clinical Trial; Product Approval and Clinical application and is the innovation model applied in the development of new advanced therapy medicinal products. Usually after market approval of a therapy in a national jurisdiction, its approval is followed in other jurisdictions, but the time and costs expended during the product development make this a difficult model to adopt. Alternatively, new models emerged trying to place the product on the market at an earlier point in the innovation process. [36]

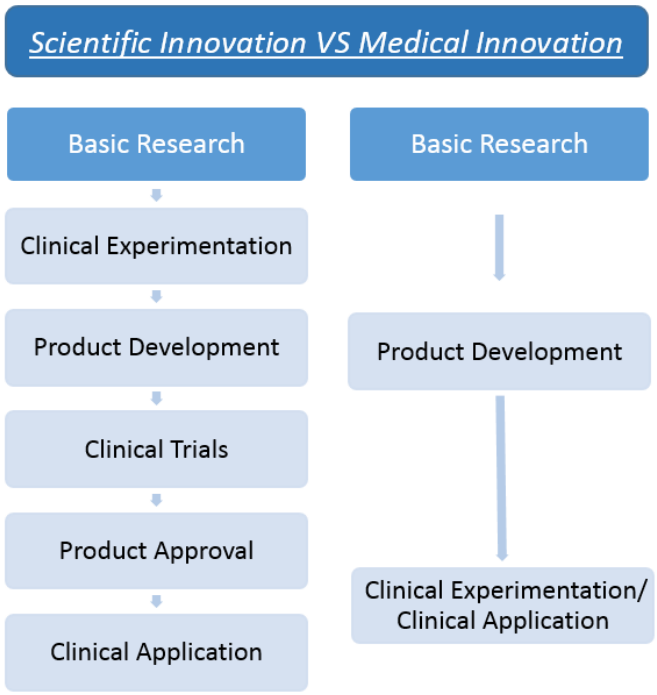

Figure 6 Direct comparison between the scientific innovation and medical innovation. (Adapted from Salter, Zhou, and Dutta.[36])

As an alternative to the difficulties associated with the use of the scientific innovation model new models emerged trying to place the product on the market at an earlier point in the innovation process. The Medical Innovation (western) model is one of those new models composed only by 3 main phases: Basic Research, Product Development and Clinical Experimentation/clinical Application. This model was created mainly based on the use of Hospital exemption (Regulation 1394/2007), the "Specials" Scheme (Directive 2001/83/EC) and others exemptions of the same type that will be analyzed in our study. The fact that in the second case the goal is to provide benefit to an individual patient instead of scientifically generalized results makes it a medical innovation instead of scientific innovation. Also this model could be considered by some researchers as a model that has lack of visibility once it does not take place inside the usual structures of research governance, the fact that this model is applied for the development of therapies to be applied in a single patient or small groups of patients and the clinician works under a single jurisdiction are other of its characteristics. The Medical Innovation (western) model, through hospital exemption allowed the emergence of therapies that will compete with the ATMP market, being placed the hypothesis of saturation of the ATMP market size, caused by the emergence of this parallel supply, being responsible for causing a negative impact in the Scientific Innovation Model I[36].

3.4. Market access strategy

Early stage market access strategy is seen as crucial to avoid the failure of commercialization of a product due to failures in understanding market access requirements. The definition of a market access strategy could help the stakeholders show the investors their capacity to obtain a commercial return on their investments as well as help establishing clinical development plan, defining manufacturing cost parameters and establishing a Business Plan. The complex reimbursement pathways are other of the parameters that could benefit from the definition of a market access strategy at an early stage[37].

In this section, an exploratory analysis was performed in order to understand what are the keys for the successful commercialization of a new cell based product, the main processes and hurdles associated with the pricing and reimbursement of this products and the main business models and strategies to captures value currently applied to cell therapies. In order to understand some of the difficulties felt during the establishment of the market access strategy it is important to identify the aspects of characterization of the cell therapy product that will impact the commercialization, therefore the distinction between autologous and allogeneic products is also present in this section. This exploratory study intends to provide information about the current situation in this sector and background for the Chapter 5.

3.4.1. Keys to successful commercialization

There are a set of requirements to accomplish in order to achieve the commercial success of a cell based therapy. The relevant aspects of the product lifecycle must be taken into consideration and the therapeutic effects are of major importance. The challenging environment of the commercialization of a new therapy product will influence its probability of success with not only the political and institutional factors having an impact in the commercialization but also the structural, regulatory and financial elements[19]. The correct characterization of the product, and aspects like product stability, robustness of the supply chain must be assured in order to achieve success for new a cell based product, the cost of goods and the cost of delivery are also parameters that will have impact on the product's final costs and influence the product's commercial success[38].

It is possible to distinguish between drivers of revenue growth, in which are included the degree of need of a product, the relative efficacy and the reimbursement flexibility and drivers of profitability in which are included the costs of goods sold. Both drivers are essential and considered keys to success. The degree of need of a treatment is a very significant factor, being a solution for a high unmet medical need is one of the keys for a successful commercialization. Proven efficacy and significant benefits in the outcomes achieved by the cell based therapy comparing with existing

therapies are also desired features, as well as the achievement of manufacture costs that allow profitability to the firm and strategies for reimbursement[5]. In Figure 7 it is possible to observe a schematic representation of the main drivers of success.

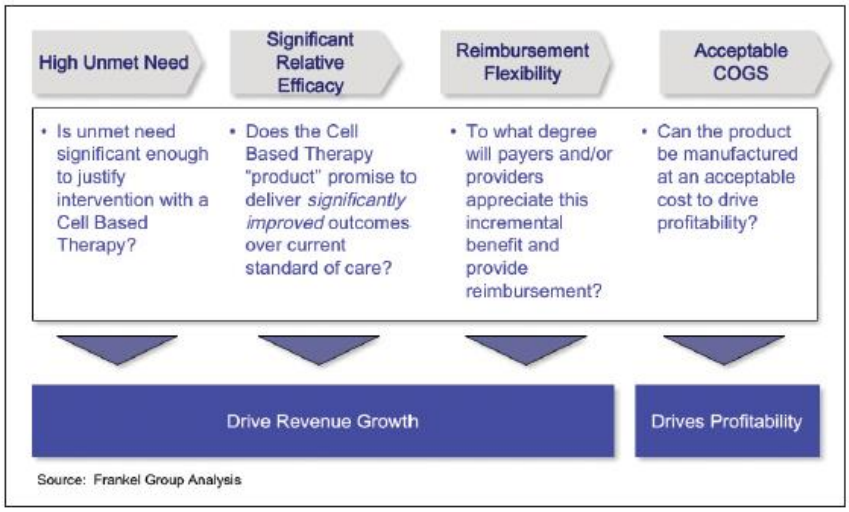

Figure 7 Four Keys to a successful cell based therapy. (Source: Frankel Group Analysis)[5]

Regulatory approval and marketing authorization are requirements that have to be combined with effective strategies for the approval of the reimbursement and with well-defined business models[39], being indispensable to have in mind the final commercialization of the product through the choices in the development process to achieve success with a new therapy.

3.4.2. Pricing and reimbursement

Market approval is a requirement for success in the commercialization of therapies, but does not guarantee it. Another important factor is the formulation and establishment of pricing and reimbursement strategies. For a therapy to access reimbursement and acceptance as a standard care, the economic aspects of production, including technologies and tools used must be taken into account since the early stages of the development.

The reimbursement and insurance coverage will be dependent on the decisions of health care providers. These decisions are made by various representative bodies, depending on the country, in some cases can even be taken at regional level or for specific hospitals, being a complex and lengthy process. In order to establish the reimbursement potential, it is important to have all the costs associated with the therapy defined, the exact indications for use of the therapy and the competing therapies[40].

The Cell Therapy Catapult, an institution who's the main purpose is provide help to cell therapy organizations, supporting them in the translation of research intro commercially viable and investable therapies, suggests a set of key elements of the pricing process and areas of focus.

According to Catapult, the target product profile must be defined and evaluated the clinical feasibility and effectiveness, the clinical and heath economic value drivers, as well as studied the minimal importance difference in incremental benefit versus standard of care/best supportive care and conducted health economic analyses. The economic analyses must include studies of the budget impact, cost-consequence, cost-effectiveness and cost-utility analyses. Uncertainty is other of the key elements to study, namely through sensitivity analyses, analogue analysis must also be performed. Lastly the analyses mentioned above should be used in exploratory consultations with key market access stakeholders[41].

A solid pricing research should establish the association between willingness-to-pay, reimbursement restrictions and could also generate knowledge useful for reimbursement strategies and arguments on willingness- to- pay. Commonly in Europe authorized ATMPS have the same process for pricing and reimbursement as other pharmaceutical products, however ATMPs present additional challenges in this area due to its often higher manufacturing costs, and extra requirements for hospital care configuration, namely related with infrastructures and qualified personal. Pricing approaches are evolving and changing from a perspective of cost-based models to competitor based models and now to value based models[42]. An illustration of the main differences of these three models is present in Table 1

Table 1 Characterization of the Cost Based Models, Competitor Based Models and Value Based Models (Adapted from Kefalas & Access 2014 and Jørgensen et al. 2015) [41,42]

Model	Cost Based	Competitor Based	Value Based
What it is	Price based on costs, expected sales, and margins	Price driven by competition	Price based on therapeutic/ economic value
Examples	Cost- Plus pricing ROI based pricing	Penetration pricing Reference group pricing	Price based on cost-utility
Comments	Becoming obsolete No longer resonates with payers	Enforced for undifferentiated products	Typical for differentiated products

	Unlicensed ATMPs (as hospital exemptions are the exemption)		

Value-based assessments permit the connection of price potential to the magnitude of the novel therapy's added-value over the standard of care (SOC), the calculation of the value is performed according to the formula (a) present below, where RV corresponds to the Reference Value, PDV to the Positive Differentiation Value and NDV to the Negative Differentiation value.

$$V = RV + PDV - ND \quad \text{(a)}$$

The chosen pricing and reimbursement frameworks for cell therapies diverge not only depending on geographic locations but also by therapy features, specifically, the size of the target population and the regulatory status of the therapy (E.g. ATMP, early access schemes, cell therapies not intended for licensing). For cell therapies approved through the hospital exemption scheme or the specials scheme commonly the price is established not on a value-based model but on a cost-plus basis[43].

3.4.3. Business Models

A business model aims to "describe the rationale of how an organization creates, delivers, and captures value" [44], and without a suitable model, the economic value yield by a technology will not be the maximum possible and the successful commercialization of a new product will not be achieved[45].

The unique characteristics and complexity associated to cell based products are leading to the emergence of new business models for regenerative medicine, different from the ones used by the pharmaceutical industries. The lack of proven business models in the cell therapy industry is one of the issues hampering the successful commercialization of cell based products, leading to an urgent need of development of new models that fit the conditions of the technological or market opportunities[46]. Otherwise, without an appropriate business model, cell therapy companies will not be able to capture value from the technology that they had developed. Oganogenesis and ATS are examples of companies that fail in the commercialization of approved products due to their business models[5].

The main payers are resistant to uncertainties and in order to mitigate the budget uncertainties felt in this industry, innovation in business models is needed. The fact that at the time of launch the

clinical and cost effectiveness profiles are not correctly and definitely established, and that there is a variation in the required dose and length of the treatment according to the patient needs are causes of budget uncertainties. Currently, the business model of one product could include a combination of the traditional business models (service, device, and off-the-shelf)[47].

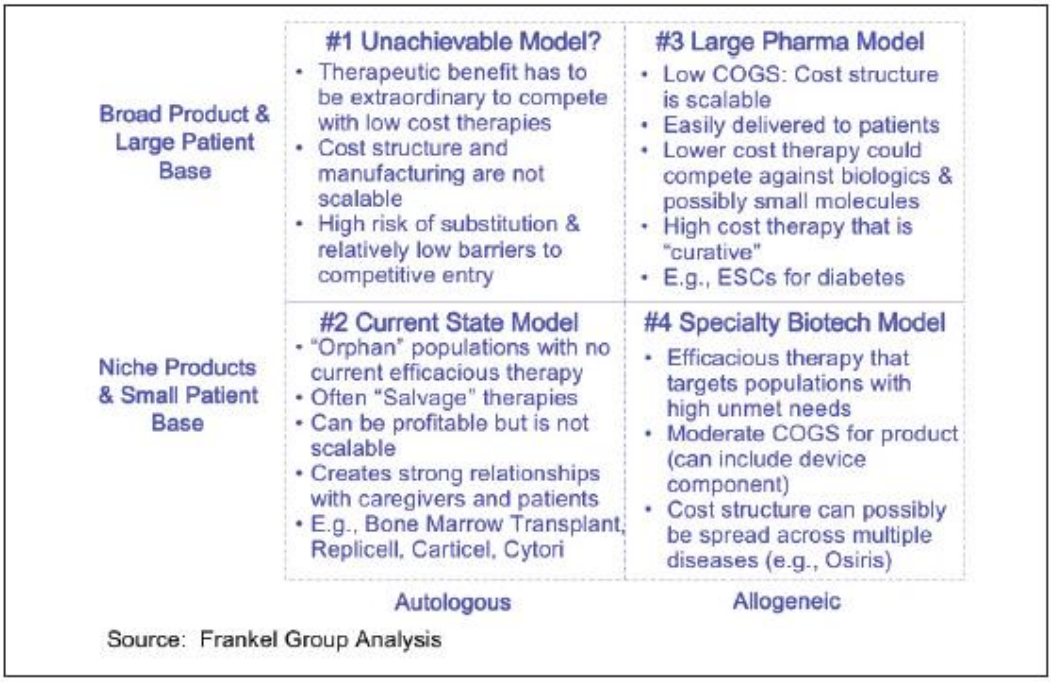

Figure 8 Cell Based Business Models. (Source: Frankel Group Analysis)[5]

In Figure 8 the available business model for the cell therapy industries are represented and the main features of each illustrated. Cell based products with different natures have different requirements therefore the figure suggests that the business models must be divided in business models for autologous products and business models for allogeneic products. It is also possible to divide the business models taking into account the market in which the products are going to be applied, in this way in the scheme presented above business models are further divided according if they are a broad product to be applied in a large patient base or niche products to be applied in a small patient base.

The business model represented in Figure 8, for a large patient base and broad product (model #1) has not yet been reached once, due to the nature of the manufacturing process for autologous therapies, these are not scalable and to compensate the high manufacturing costs of the therapy, this would be more effective than the existing ones for the same disease. The second business model, for an autologous and niche products is mainly applied to orphan drugs for conditions which have no effective treatment available. This type of business model favors the establishment of relationships with caregivers and patients due to the type of treatment. The third business model

corresponds to the large pharma model. Allows the scalability of the manufacturing process and therefore a cost reduction, also allows an easy deliver to patients and competition with biologics and small molecules which is possible if the therapy is "curative". The fourth model for allogeneic therapies could be applied to cell based therapies that target unmet medical needs[5].

A study developed in 2012 has identified a set of strategies that could help cell-therapies to capture value in the commercialization of new therapies. The identified strategies were: Orphan designation, High impact therapies, Platform solution, Therapy kit, and Incremental Solution[48].

Targeting orphan diseases allows expedite regulatory approval combined with a prolonged exclusivity in the market. This strategy stimulates the achievement of the clinical proof of concept for a determined disease. Therapies that target unmet medical needs, chronic diseases and others where there is an urgency to the emergence of new treatments was also identified as a strategy that could permit easy access to financing. Platform Solution, which consists in the development of a unique solution for multiple applications allowing the target of multiple diseases being an advantage that allows the production of multiple cell lines to address different medical needs. Therapy Kit refers to the development of a kit where the cells from the patients are placed on-site and the final therapeutic product is administrated to the patient, having as advantages ease of administration, and no need of specialized cell processing infrastructures, once the kits are stored and used as part of the procedure resulting in a reduction of costs. Lastly, incremental solutions consisting in the target of solutions considered incremental innovation, allowing technological improvement and valuation of an existing product, where also identified as strategies to capture value. The fact that this type of product have regulatory routs and distribution channels are already established and that medical doctors are already familiar with the therapy are the main advantages of these solutions [48].

3.4.4. Characterization of the cell based product

In order to select the best business model to a cell based therapy all the relevant aspects and characteristics of the product through its lifecycle should be considered, and the funds available through the entire process. The characterization of the respective technology, namely the type of cells used, the source of the cells, the manufacturing process and the type of therapy (Autologous or Allogeneic) are crucial in the selection and design of the business model. The characterization of the market of the final product (dimensions and classification of the market), namely, definition of the customers of the therapy, consumers and the possibility or degree of competition are also important aspects. The final features of the product, namely, the availability of the final product, the rout of administration, the package used, the store and rout of distribution will also have an impact in the business model [47]. In Figure 9 the keys for the correct characterization of the product are summarized.

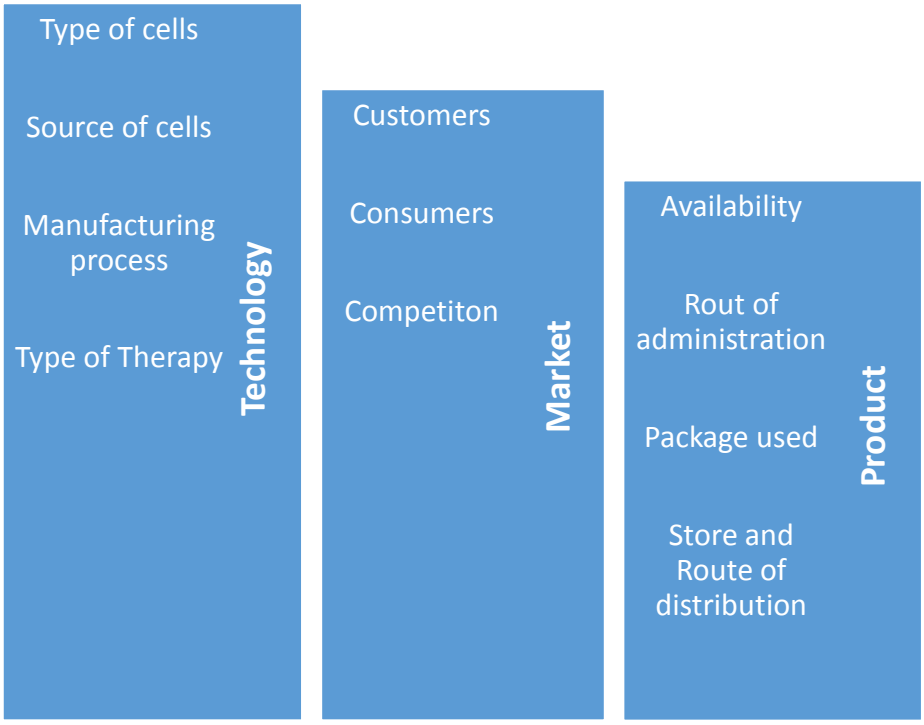

Figure 9 Keys for the characterization of a cell based product

3.4.4.1. Autologous vs allogeneic products

A cell based therapy is considered autologous when is constituted by manipulated cells collected from the patient who will receive the therapy, while in an allogeneic product the source of cells is different from the patient who will receive the cell therapy, whereby it allows the treatment of many patients with cells from the same source and the treatment is available to apply when need by the patient [48,49].Figure 10 contains a simplified schematic representation of the different scales and complexities of both types of therapies.

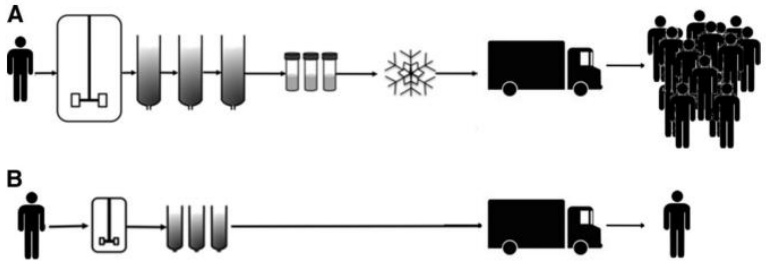

Figure 10 Schematic representation of allogeneic cell therapies business models(A) and autologous cell therapies business models (B) (Source: Foley & Whitaker 2012)[49]

The differences between both types of treatments will lead to different requirements related to safety, efficacy and the approaches to manufacturing and distribution of the therapies.

Consequently the different challenges in development and commercialization of both types of therapies will result in the need for different business models. The challenges are higher for autologous treatments where the advantages for the patients could in some cases be superior but faces different challenges because of their regulatory compliance process, clinical delivery logistics and ultimate clinical and business viability [50,51]. Time of delivery is a very important factor to consider for cell therapy treatments due to the nature of the final products, since the materials collected from donors and the final therapies have really limited shelf-lives (order of days) except if frozen[52].

Autologous cell therapies are not “of the shelf products”, the need for cells collection from the patient implies proximity between the production site (research hospital, for example) and patients or a system of collection of cells from the patient and distribution of the final therapy highly efficient, whereby the delivery system of these products could be complex. The non- existence of risk of immunological rejection is the biggest advantage of autologous therapies, but the manufacturing and delivery processes present additional challenges comparing to allogeneic cell based therapies[50]. As disadvantages autologous therapies have the fact that the manufacturing process is not scalable not allowing the reduction of the cost of products due to a large scale manufacture, instead there is a need to scale-out the process of production[53].

Allogeneic therapies allow the adoption of business and supply models comparable to the ones used by conventional biopharmaceutical companies, presenting commercial viability[54].These therapies are ready to apply, the manufacturing process is scalable and allow the possibility to compete against biologics and small molecules[53]. The risk of immunological rejection is the major challenge of allogeneic cell based therapies excepting some cases, and the use of long-term immunosuppression increases the risk of morbidity and mortality. The establishment of safety increases the complexity of the regulatory pathway being required the assessment of safety and integrity of the samples along the value chain[48]. The distribution of non-cryopreserved allogeneic therapies, with shelf lives of days also could lead to the necessity of maintain constant the level of production even when there are variations in the clinical demand, increasing the overall product cost and may have as a consequence the waste[49].

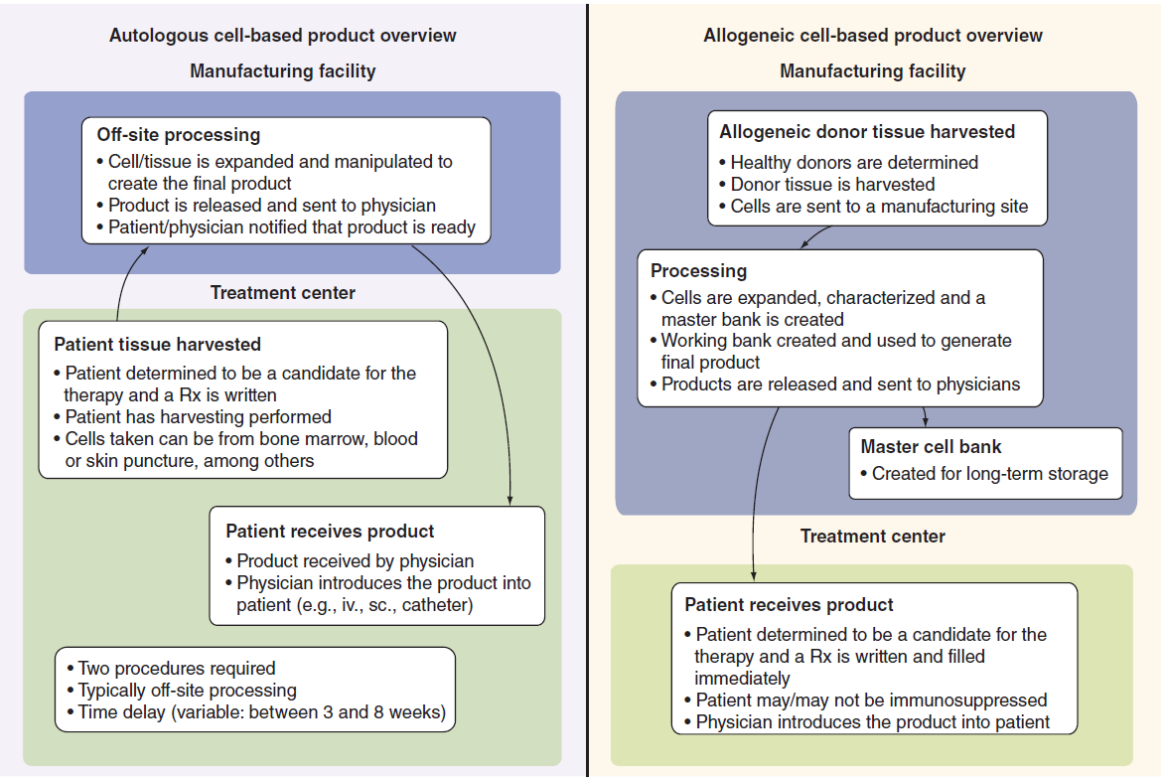

Figure 11 Autologous and allogeneic cell-based business models, where. Iv.: Intravenous; RX.: Prescription; sc.: Subcutaneous (Source: Smith 2012)[55]

In Figure 11 is possible to observe an overview and description of the processes related to an autologous and allogeneic products. As represented, for an autologous cell-based product, the first step is the harvest of the patient's tissue in a treatment center, followed by an off-site processing in the manufacturing facility, where the collected tissue is expanded and manipulated in order to create the final therapy which is then forwarded to the treatment center, where the product is received and applied to the patient. In this process is important to highlight the number of procedures required and the existence of time delay, which can have a duration that varies between 3 and 8 weeks. For an allogeneic cell-based therapy, the donor tissue is harvested in the manufacturing facility followed by the processing where the cells are expanded and manipulated; then either the product is distributed to a master cell bank or it is sent directly to a treatment center where the patient receives the treatment[55].

In Figure 11 there is an illustrative representation of the ratios between the revenues and the cost of goods of two hypothetic cell based products, an autologous therapy and an allogeneic therapy. Both therapies are supposed to be applied in the same indication, have the same efficacy and safety and the same price per patient at launch. Due to the nature of the different therapies, the cost of goods are superior for the autologous product, and although both therapies may compete

for a limited number of patients when this number increases the possibility of economies of scale represents an advantage in case of a large number of patients[55].

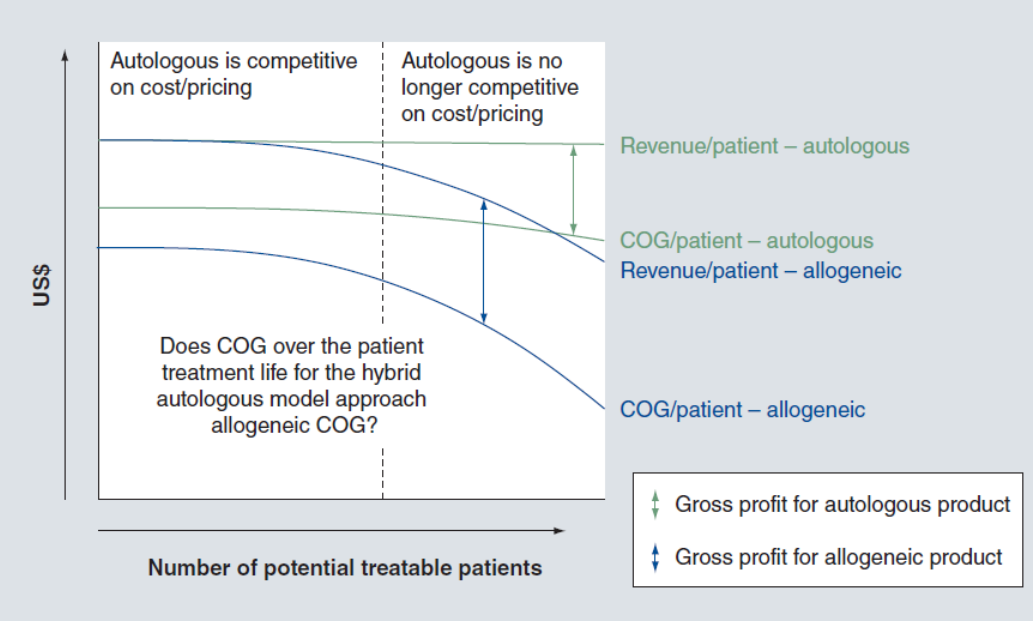

Figure 1 Relative cost of goods versus profitability by type of therapy. COG: Cost of goods. (Source: Smith 2012)[55]

3.5. Value Chain

A value chain corresponds to the entire set of activities required to bring a new product or service to the final consumer to its consumption or recycling, since the beginning and going through all stages of the development process, storage and transportation[56]. An understanding of the value chain of a product its essential once it will impact the potential of the final product, for this reason a brief description of the main activities in the a value chain for cell therapies will be present in this section. In Figure 12, a generic value chain is schematized.

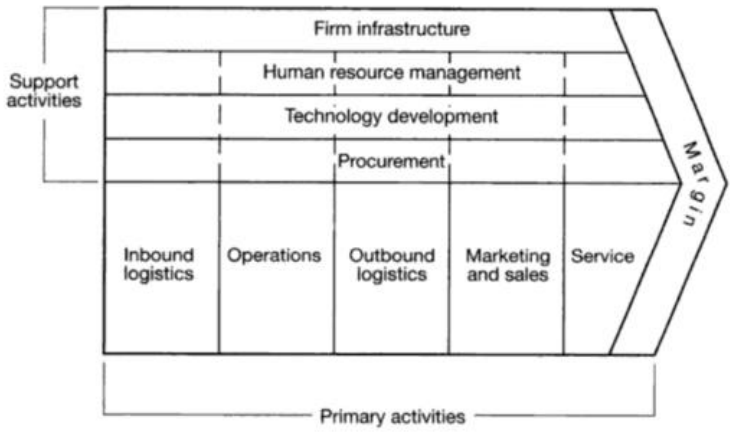

Figure 12 Value chain. (Source: Porter, M.E. 1985)

We can distinguish two main types of activities in the value chain, i) primary activities and ii) support activities. Primary activities include inbound logistics, operations, outbound logistics, marketing and sales and services; the support activities enclose firm infrastructure, human resources management, technology development and procurement. The execution of these activities in a more efficient or differentiated way than its competitors is one element on the competitive advantage by firms[57].

Having in mind the value chain of a cell therapy, the reception of the donor cells and other required raw materials, their storage and dissemination are part of the inbound logistics, where the main challenges are the requirements related to the specifications for cell therapy culture, conditions that are not easily scalable, and the requirements related to tracking of the starting cell material. The manufacturing process of the final therapy is the operation activity, which is followed by the outbound logistics activities composed by the therapy storing and costumer or patient distribution. Due to the nature and characteristics of cell based therapies, the outbound logistics strategy of a cell therapy company could have huge impact in the success of a new treatment. The marketing and sales activities will occur among interest groups, general public and media, achieving the customer and patient treatment, namely through medical procedures, which also integrate the value chain of a cell therapy company. The way how these two main types of activities are performed will affect the firm profits, and need to be accounted in a business model.

A generic value chain for cell therapies is present in Figure 13, where the external environment and existing relations between Funders, Regulators and Policy Makers are represented as well as the relations with the final patients. In the specific case of cell based products the value chain depends on the cell donors, on the researchers in which are included not only the basic researchers like universities but also the translational research that will establish connections with the Non Medicinal product suppliers and with manufacturers within the Medicinal product suppliers. The producers have relations with the distributers that will be responsible to deliver the therapy to the

health care providers and those to the final consumer, in this case the patients. The patients in turn would be influenced by the relationships with the general public, media and interest groups, and is important to highlight the existing influences between funders, regulators and policy makers in the establishment of the value chain[58].

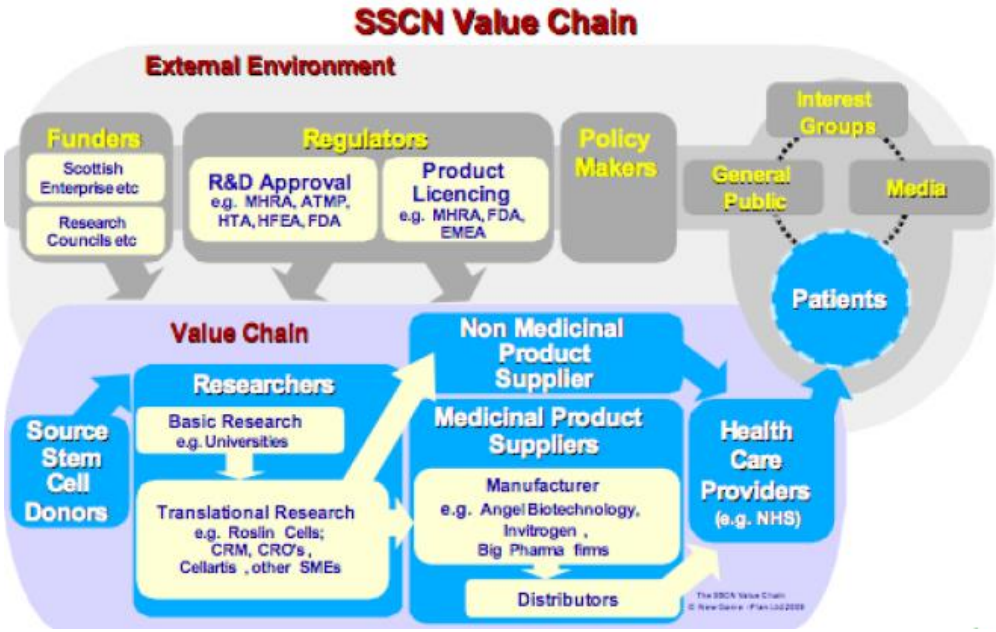

Figure 13 REALISE Generic Value System environment. (From Tait et al. 2010)[58]*.*

3.6. Supply Chain

Supply chains are complex networks of interdependent organizations of variable complexity and dimensions. The term was defined by J. Aitken as "A Network of connected and interdependent organizations mutually and co-operatively working together to control, manage and improve the flow of materials and information from suppliers and users"[59] .Along with logistics, supply chains have the potential to help an organization achieve cost and value advantage, occupying an important position with respect to the potential success of a product[57], being this the main reasons that led us to introduce an analysis about supply chains in our study. Flexibility and redundancy are important features of a supply chain in order to respond efficiently to possible challenges and complications without affect the sustainability of the entire chain[60].

The fact that the supply chains supporting cell therapy industry is still currently considered fragile and immature increases the risk of disruption and jeopardizes the sustainability of the cell therapy industry. The unavailability of one element of the supply chain will require new changes, testes and demonstration of comparability, whereby, to avoid exposure to the risks companies assess the

possible rupture of all inputs of the supply chain for its process, including consumables, reagents other equipment and human resources[61].

The nature of this technology, namely the manual, human-dependent and exposure of the product in some of the manufacturing process steps could affect the quality of the final product requiring a very stringent regulation. The requirements related to the compliance with the Good Manufacturing Practices (GMP), clean room for manufacturing, traceability records, shelf-life and process standardization makes the supply chains in the cell therapy industry highly regulated. The complexity of these supply chains is also increased by the time sensitive, temperature sensitive and non-linear features of the therapies, making it a challenge to ensure the reliability of the supply chain during scale up and scale out processes[62].

The cell therapy supply logistics involves costly processes, the shipping costs for products as cell therapies that could not be preserved at room temperatures and that need to be stored in freezers or in liquid nitrogen could increase the transportation costs up to five times. The preservation and shipping at room temperature of cell therapy products would be a highly disruptive process[60]. The alteration of manufacturing process ad hoc is not allowed and the supply chain has to be established during the development, as part of the approval process, in order to guarantee that the product has no contamination or even different composition from the approved product[63].

According to the existing regulation in Europe and in the United States, in order to introduce any change in the infrastructures or processes involved in the production or distribution of a cell therapy, namely, introduction of multiple sites of production, reconfiguration of facilities or modifications in locations or suppliers that affect the supply chain, the demonstration of product equivalence is required[54]. This requirement imposes that the supply chain should not suffer modifications making indispensable that the suppliers are analyzed and its risk of bankruptcy or discontinuance of its products to be analyzed in an attempt to minimize as possible the problems that producers would have. Redundancy is an important way to minimize risks but due to the low maturity of the industry and the predominance of small companies this redundancy is not always secured, increasing supply chain related risks.

According to Teng et al, as illustrated by Figure 14, it is possible to classify the supply chain uncertainty with the help of a framework in four main classes, depending on the degree of the supply uncertainty and on the degree of demand uncertainty. The strategy applied to the supply chain in order to minimize the negative effects of this uncertainty will take into account several aspects, and the supply chains would be characterized as Responsive, Flexible/Agile, Efficient and Risk-Hedging and would be characteristic and more or less appropriated to different clinical products depending on their features.

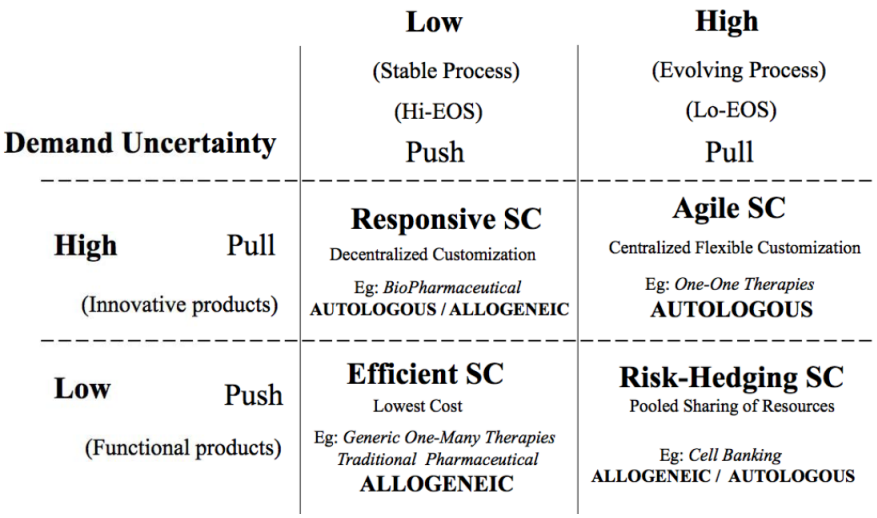

Figure 14 Therapeutic Medicine Supply Chain Uncertainty Framework. (Source: Teng et al. 2013)[63]

Considering the Demand Uncertainty as low and the supply uncertainty as low, in a push-push based supply chain strategy the management decisions are taken according efficiency, this strategy could lead to inefficiency meeting changing demands and possibility of obsolescent inventory because of the high reaction times to possible fluctuations in the markets. Currently, this push strategy is characteristic of traditional pharmaceuticals. Classifying the supply uncertainty as low and the demand uncertainty as high, a push- pull strategy would be adequate with the products being shipped to decentralized warehouses allowing an efficient customization response to the requests. Dealing with high supply and demand uncertainties will require that the production would be triggered not by forecasts or studies but by clinical requests, leading to low inventories and consequently requiring flexible responses of the supply chains in order to respond readily to demands. Considering the demand uncertainty as low and the supply uncertainty as high, a pull-push Strategy would allow that the inventory is pooled into decentralized locations allowing the maintenance of determined levels of inventory reducing the risk of coverage failure[63].

Uncertainties associated with the demand and supply of the cell therapy industry could also be responsible for threat and destabilize the cell therapy markets jeopardizing future investments from investors.

4. Regulation

The nature of this technology makes the cell therapy global market a highly segmented, with products from different sources and targets and with experts defending that hardly a single approach to regulation could be an effective solution[64].

In this chapter we highlight the most important aspects of regulation affecting the Cell Therapy industry, which is highly regulated. The approval process of a cell therapy based products in Europe will be present as well as other existing regulatory exceptions such as the *Hospital Exemption* and the *Specials Scheme*. The impacts and main critics to this exceptions from industry stakeholders and potential impacts to the cell therapy markets were also studied as well as the requirements established by the regulation and required data for approval that will also be presented in order to contextualize and facilitate the reading of the Chapter 5.

4.1. European Regulatory Framework

Encouraged by the excellence existing in the basic science and unmet medical needs, Europe has established an important role in the recent years, in the development of research in advanced therapies and in the attempt of the translation to the market of cell based products. In order to allow the safe and efficient introduction of advanced therapies in the healthcare system and to try to get the most potential offered by these therapies, regulatory pathways were developed and implemented aiming to ensure the quality of the products and the compliance with safety standards of the treatments[3].

The European Medicines Agency (EMA) started activities in 1995 and is a European Union (EU) agency whose main goal is to ensure the protection and promotion of public and animal health. EMA assures the evaluation of medicinal products and the results are used by the European Commission to attribute a marketing authorization in the European Union. In addition, the agency is responsible for the supervision of the safety and efficacy conditions (pharmacovigilance) of medicines already authorized in EU[65].

4.1.1. Advanced Therapy Medicinal Products

In Europe, cell based therapies including substantially manipulated cells are included in the advanced therapy medicinal products (ATMPs) classification. The Committee for Advanced Therapies (CAT) within the European Medicines Agency is a multidisciplinary committee responsible for the assessment of requirements associated to the central authorization of these medicines and for the

definition of the conditions for marketing authorization, supervision and pharmacovigilance of advanced therapy medicinal products in all Member States of the European Parliament[10,66]. The rules related to the development, production and commercialization of ATMPs are established by a set of Directives: Directive 2003/63/EC (amending Directive 2001/ 83/EC), which describes cell based therapies as clinical products, Directive 2001/20/EC , which establishes that these medicines must be subjected to clinical trials and presents the requirements for approval of the related clinical trials; and Directive 2004/23/EC , which defines and imposes the requirements of standard quality, donation safety, harvesting, tests, processing, preservation, storage, and distribution of human tissues and cells[17,67].

It is possible to distinguish four different types of advanced medicinal products: gene-therapy medicines, somatic-cell therapy medicines, tissue-engineered medicines and combined advanced therapy medicines. In Gene therapies recombinant genes are used in order to promote the diagnosis of a certain condition or obtain a therapeutic effect, namely in genetic disorders but could also be applied to other conditions. Somatic-cell therapies consists on the use of manipulated cells or tissues, with altered biological characteristics for the treatment, diagnosis or prevention of diseases. In Tissue-engineered medicines modified cells or tissues are used to promote regeneration of a human tissue and in combined advanced therapy medicines, medical devices are part of the medicine[68]. In Figure 15 it is shown a representation of the regulatory pathways for ATMPs in Europe demonstrating the regulatory milestones as well as the development milestones until the product reaches the market authorization[27].

In order to achieve a marketing authorization application, the cell therapy product must undergo rigorous testing phases where risk factors are analyzed, as well as pharmacodynamics, pharmacokinetics and the toxicology of the therapy. During the non-clinical development phase the main goal is the demonstration of the proof-of-principal and product characterization. Efficacy and safety are the main parameters examined and, at this stage is also important the definition of the dose of the therapy to be applied in the clinical population during the clinical trials. The length of phase I is usually of several months and has the participation of a small amount of people (between 20 to 80 people). In this phase the first administration to humans occurs and the main goal is to ensure that the therapy is safe. Multiple doses can be tested in order to check for dose response, namely the Minimal Effective Dose, the Optimal Effective Dose Range and the Safe Maximal Dose, ensuring tolerability and defining side effects. Phase II length is superior (approximately 2 years) and the therapy is applied to a higher number of patients (several hundred). Although ensure safety at this stage is important, the main goal at this point is to ensure Efficacy of the therapy. Phase III can last up to 4 years and at this stage the therapy is applied to a greater number of people then at phase II (up to several thousand). Pharmacovigilance is the Phase IV main goal. This phase aims to monitor the long term effectiveness of the therapy and has a duration much superior to the previous[69].

Although there are many common aspects between a clinical trial for a cell therapy development and clinical trial for traditional drug, there are some aspects that are characteristic of developing cell therapies. Unlike the usual, in the case of cell therapies, the first administration of a therapy in human occurs in patients and not in healthy volunteers. The need for rigorous evaluation of parameters as cell survival, persistence and engraftment requires always the existence of a long term follow-up and due to the nature of this type of therapies the integration between the clinical and manufacturing plans are critical. Other logistic aspects as clinical staff training in administration of the therapies or cell donation, testing and traceability also have a very high importance in this type of clinical trials[70].

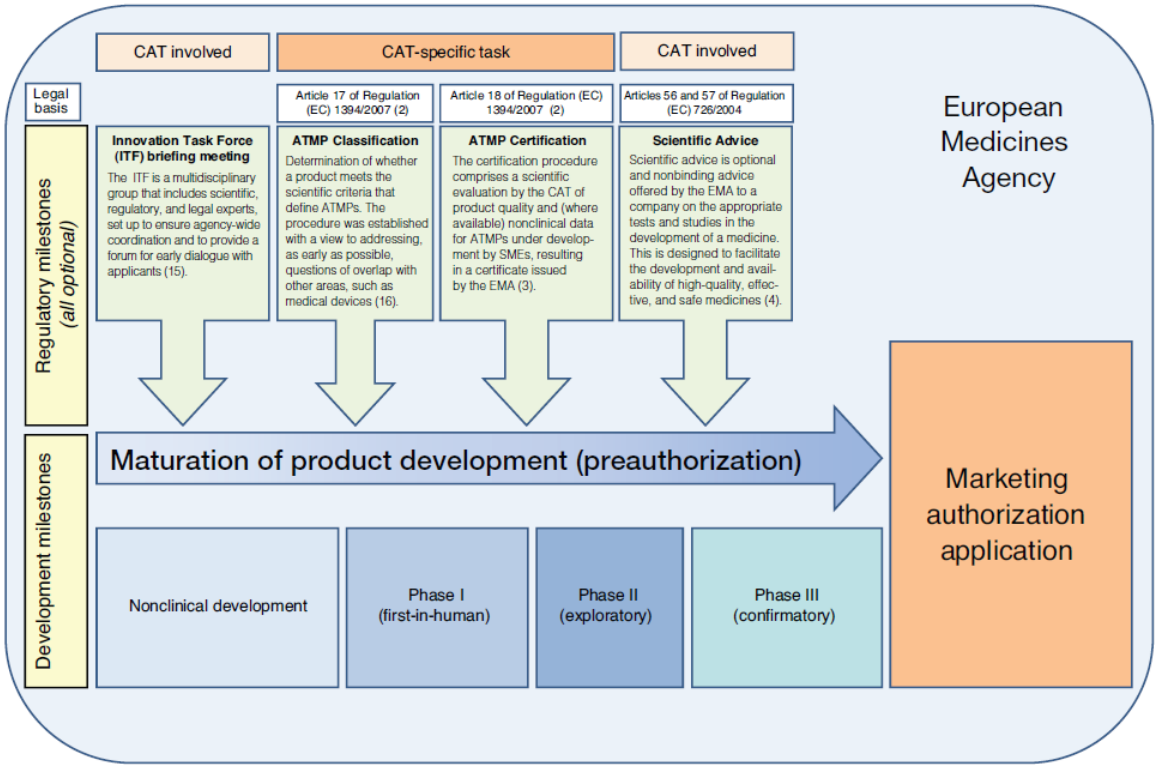

Figure 15 Regulatory pathways for ATMPs in Europe. Development milestones and Regulatory milestones. (Source: Maciulaitis et al. 2012) [27]

4.1.1.1. Data and documentation required

In order for a new cell therapy to be approved the guidelines on good clinical practices (GCP) and good manufacturing practices (GMP) must be followed and a set of documents containing traceability records and other information about the therapy and associated processes are required to all the participants in the approval process. Essential documents are the ones responsible to demonstrate compliance with the regulatory requirements and GCP standards from the investigators and sponsors and also to monitor the processes[67].

In order for the clinical trials to begin, documentation containing details of the process and responsibilities of the manufacture of the ATMP, of the investigator and institutions of the sponsor and of the tissue or blood establishments or animal facilities are indispensable. The documentation of the planned follow up strategy for the ATMP are also required as well as an evaluation of the risk. During the clinical trials, any updates to the details of the process and traceability records linking the sources of the donated must be documented as well as updates to the follow up strategy and traceability records since the manufacture of the ATMP to the patient (Including patient identification and medical files). After the clinical trials the information mentioned before must be delivered along with the final traceability records data related to follow-up procedures, namely related to the safety follow up and efficacy follow up[71,72]. Although not very different from the currently required to the pharmaceutical industry this documentation is a major burden for the stakeholders in the cell therapy industry.

4.2. Hospital exemption

The regulatory exception “Hospital exemption” was created with the purpose of allowing patients that suffer from a rare disease with no established cure or treatment to benefit from a therapeutic alternative. This exception aims to provide patients under exceptional circumstances a custom-made, innovative and individual treatment that includes cells tissues or gene therapy, when the low incidence of the disease doesn’t justify or permit the development and commercialization by the regular pathways[7], high unmet medical needs and no authorized ATMP alternatives available are the other cases that this exemption aims to address[73].

For the European Union, Hospital exemptions are defined in the Article 28, Directive 2001/83/EC as “Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient. Manufacturing of these products shall be authorized by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorization is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency”.

In October 2012, a report on Hospital exemption for advanced therapy medicinal products was prepared by a pharmaceutical committee from the European Medicines Agency (EMA). This report contained the number of products legally on the market of each member state, which of these products were prepared on a routine basis and which of these products fell under the hospital exemption. In addition, information related to the criteria applied for products under the hospital exemption were examined. The results showed that in a total of Twenty-seven countries, ten had ATMP legally on the market, being ChondroCelect the most common product. Also, six of the analyzed countries had ATMP hospital exemption. Different countries owned different criteria for Hospital Exemption namely, the frequency of production and the total number of products that can be produced. Some countries are still developing the guidelines related to this regulatory exemption[74]. Netherlands regulation, for example imposes a maximum of ten patients year per license, other countries don't establish any limits[75].

In July 2015 a survey conducted by MedNous performed to twenty-two national regulators asked about the number of hospital exemption granted. The survey was answered by eleven agencies of which four had approved authorizations. The countries with the highest numbers of hospital exemptions were Germany (seven authorizations), Sweden and Denmark) with three authorizations and Ireland made one authorization[8]. In is possible to observe data related to countries, numbers of exemptions authorized and related Time Period,

Hospital exemptions in the European Union

Country	Authorising body	Exemptions	Time Period
Germany	Paul-Ehrlich Institut	7	2009-present
Sweden	Medical Products Agency	3	2011-2013
Denmark	Danish Health and Medicines Authority	3	2014
Spain	Spanish Agency of Medicines and Medical Devices	None	2009-present
Portugal	Infarmed	None	2009-present
Czech Republic	State Institute for Drug Control	None	2009-present
Ireland	Health Products Regulatory Authority	1	2014
Estonia	State Agency of Medicines	None	2009-present

The data comes from a MedNous survey of EU regulators

Figure 16 Hhospital exemption in European Union. (Source: Mednous 2015)[8]

4.2.1. Main criticism on hospital exemption

Although the need for hospital exemption is recognized as a useful tool, allowing some patients to have access to innovative treatments, it is also associated with some criticism and debate. The lack of clarification about the exact definition of hospital exemption, and the use of ambiguous terminology in the existent legislation were responsible for raising some questions among stakeholders within industry and academia.

The current legislation does not specify what is understood as “industrial process” or the meaning of “custom-made product”. The non-definition of “specific quality standards” are controversial and the use of the expression “non-routine basis” also gives rise to the possibility of different interpretations by stakeholders and Member States, as it does not establish, for example, a maximum limit of procedures in some member states[67,76].

Different interpretations of the legislation between member states increases the uncertainty and could be responsible for the fragmentation of the European Cell therapy market, increasing the risks of reduction of the number of applications for marketing authorizations, as well as an increase the uncertainty associated with the forecasts related with costs and resources, performed by the cell therapies companies[77].

The use of products from Hospital Exemption to the treatment of patients with conditions potentially treated with centrally licensed products leads to debate. The high investments performed by companies who develop Advanced Therapy Medicinal Products, namely in clinical trials, and regulatory requirements are such that the final prices for their products are higher that the prices charged by hospitals[8]. This difference in the development costs may be seen as a competitive disadvantage for companies with therapies in commercialization. The quality requirements for the development and manufacturing of cell based therapies under hospital exemption vary because these requirements are established by each specific member state. The different member states could define different requirements. These different standards are often seen as a competitive disadvantage by the cell therapy companies[9] which is caused by the different manufacturing costs directly influenced by the price needed to cover all the requirements requested and consequently high final prices in the cell therapy products.

As proposed solutions to the divergences related to the existence of Hospital exemption, industry members argue that the possibility of using these therapies in hospitals should not be allowed when there are approved therapeutic alternatives. In addition, they defend the attribution of more incentives to the use of the centralized procedure and the harmonization of the standards and requirements applied by the different member states[8]. This market distortion and competitive disadvantages are seen as a major factor preventing the development and use of non-exempted therapies and investments in the industry, and requires the clarification through legislation [7].

4.2.2. Hospital exemption and the specials scheme

Specials are included in the regulation through the DIRECTIVE 2001/83/EC, Article 5 1, in which: “A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health-care professional and for use by an individual patient under his direct personal responsibility”. This regulation allowed the establishment of the specials scheme, permitting the access of patients to innovative treatments that were not approved by the conventional pathways mentioned before. Similar to hospital exemption also the specials scheme is a regulatory exception[78].

Although the Hospital exemption and the special schemes could present some similarities they also present a substantial differences in the regulatory requirements. Unlike what happens with hospital exemption, the products developed under the Specials Scheme in the United Kingdom could be prescribed not only by medical practitioners but also by dentists, pharmacists, nurses and other supplementary prescribers. Under this scheme a product can be developed and manufactured in the, member state or imported into it and there is no obligation to be used in a hospital, also the existence of the product under the Specials Scheme is only valid in the absence of an equivalent product with market authorization that fulfills the needs of the patient’s condition[79]. In the United Kingdom, only the institutions granted with a specific license by MHRA that guarantees that the manufacturing process occurs under good manufacturing practice conditions are allowed to produce products under the exemption schemes mentioned before[80].

Summary of some of the main differences in scope between the hospital exemption and "specials" schemes	
Hospital exemption	**The "specials" scheme**
The ATMP must be prepared and used in the same EU Member State	Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK
The ATMP must be commissioned by a medical practitioner	Products can be prescribed by doctors, dentists and supplementary prescribers
The ATMP must be custom made to meet an individual prescription and preparation must be on a "non- routine basis"	There is a special needs test (interpreted to mean the absence of a pharmaceutically equivalent and available licensed product)
The ATMP must be used in a hospital	There is no stipulation as to location

Figure 17 Summary of some of the main differences between the hospital exemption and "specials" schemes (Source: MHRA 2010)[79]

4.3. Cell Therapies in Europe and in the United States, dissimilarities

In the course of our analysis, we identified significant differences in the context of industrial development for cell therapies in different world regions. In this section we look closer at differences between Europe and in the US, as the regions where this development is being done in a comparable manner.

In the United States the regulatory body responsible for the production and marketing of cell-based therapies is the Food and Drug Administration (FDA). This regulatory body is responsible for the regulation of Human Medical Products which could be divided in three main sections: Drugs, Devices and Biologics. Biologics is the category in which cell-based therapy products are included. This category also includes human cells, tissues, and cellular and tissue-based products (HCT/Ps). Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient are under the Definition: 42 USC 351 (i)[81].

Although there are differences in regulatory frameworks in Europe and United States both of the responsible agencies are in contact in an attempt to harmonize regulations and approval processes[10]. There are significant dissimilarities between the Europe and Unites States related with the main regulations. In the United States the Centre for Biologics Evaluation and Research (CBER) and the

Office of Cellular, Tissue and Gene Therapies (OCTGT) are the other authorizing bodies while in Europe the secondary authorizing bodies are the national health authorities. While in Europe the process for approval of clinical trials is responsibility of the health authorities of the respective member state, in the US the authorities responsible are the National Academy sciences and the National Institutes of Health. Also in Europe unlike in United States there is no differentiation between private or public funding[82]. This information in synthetized in Figure 18.

Another important difference to be considered for our analysis is that in the US, there is no Hospital Exemption scheme, instead doctors could apply not approved cell based therapies containing more than minimally manipulated cell products through two different pathways, i) expanded access to investigational drugs and ii) biological products for treatment or off-label prescribing. The first option allows the administration of cell based therapies to patients if these therapies are being tested in a clinical trial and if the administration does not cause interferences in the clinical trials. The second possibility, assumes that physicians can be trusted to use their professional judgment in deciding how to treat their patients[10].

Table 3: US vs Europe – Key differences

	US	Europe
Overall responsible authority	FDA	EMEA
Access to funding	• Federal – NIH • Private	No differentiation between public and private funding
Responsible body for approval of clinical trials	• NIH (if federally funded) • National Academy of sciences (central framework adapted by individual states)	Health authorities at national level
Other authorising bodies	• Centre for Biologics Evaluation and Research (CBER) • Office of Cellular, Tissue and Gene Therapies (OCTGT)	Refer to national health authority websites
Main regulation	Public Health Act, Section 351 – biologics	Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products
Provision of scientific advice	The Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC)	• Committee for Medicinal Products for Human Use (CHMP) • Committee on Advanced Therapies (CAT), EMEA

Figure 18 US VS Europe- Key differences. (Source: Deal 2009)[82]

In the graphs of Figure 19, it is possible to observe the amount of studies started each year and the phases in which they are. The comparison of the graphs corresponding to information from the United States (US) and from Europe (EU) demonstrates that since 2004 and until 2014 the amount of cell therapies started each year is superior in the United States. In addition, the most prevalent phase of the clinical trials is phase 2, and the less predominant is the phase 4, in both US and EU, what could be due to the development phase of the cell therapy industry which is still recent, as mentioned before.

It is also important to highlight the high number of cell therapy studies without information about the correspondent phase[3].

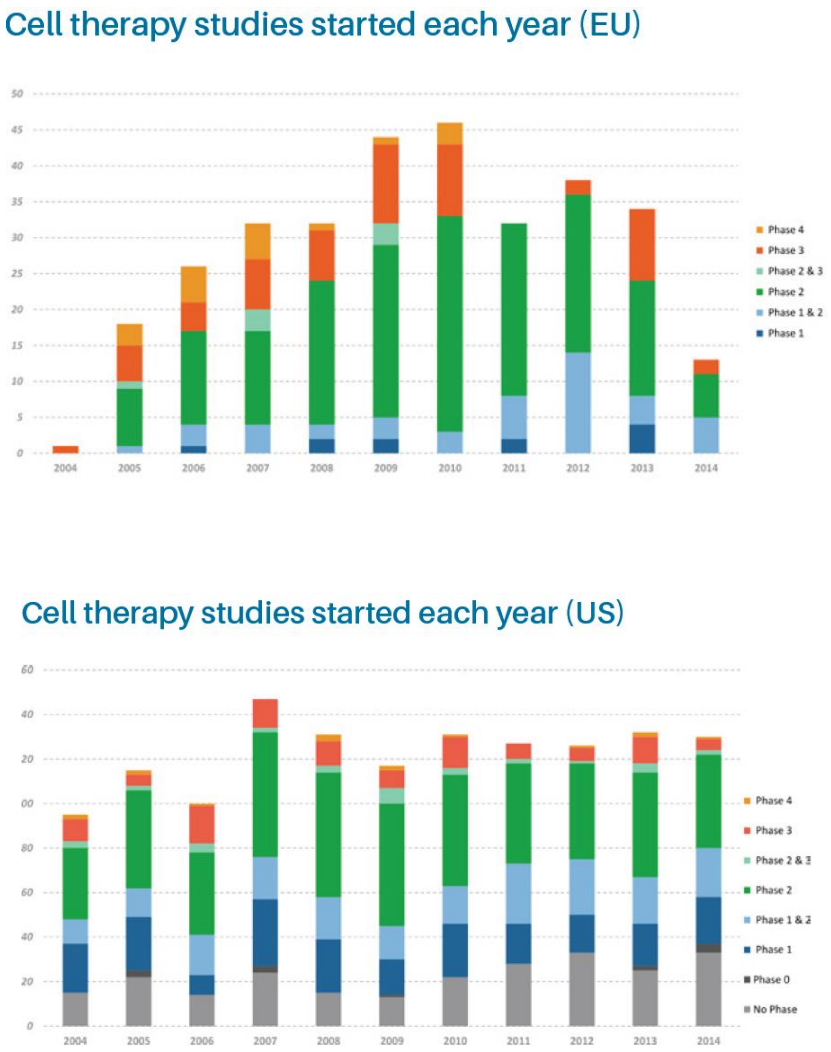

Figure 19 Cell Therapy Studies Started each Year in EU vs US (Source: European biopharmaceutical Enterprises & Transformation 2015)[3]

5. Data Analyses and Results

The interview process described and the interview protocol present in Supplementary Data section allowed the collection and analysis of data from several industry stakeholders, academy and people from regulatory bodies responsible for the regulation of the cell therapy industry in Europe. The exploratory questions performed and the previous research allowed the collection of a significant amount of qualitative information. The open-ended nature of the survey aimed to explore, find explanations or justifications and if possible support or disprove previous established ideas, therefore the verified diversity in the obtained responses and the multiplicity of the collected explanations from the interviewed were expected.

The use of mapping methods in this study was driven by the need of a qualitative data structuring method to apply in order to analyze complex information. In our study, conceptual mapping will appear as an exploratory tool permitting the mapping of ideas and shape graphical representations of the interviews perceptions and other relations of influence perceived through the literature review analyses, with the links between ideas or concepts representing a possible relation of influence.

In the next sections is possible the observation of conceptual maps composed by multi -directional networks of concepts or ideas related to the topics under analyses and drawn from the information collected during in the investigation. In order to allow a direct comparison between the points of view from the different sectors and a quick access to the main thoughts obtained in each question, summary tables will be also presented in each section. A case study will be presented also in this section in order to provide real examples and contextualize the commercialization of an approved cell therapy with the difficulties and experiences felt during the commercialization of a cell based product.

5.1. Challenges in the cell therapy industry

The main challenges of the cell therapy industry was one of the considered themes in our study, being one of our goals understand if the challenges mentioned by the people from the different industry sectors showed similarities or if the opinions diverged according the industry sector. According the responses it was identified that the main challenges could vary according the different geographic regions. The fact that the results of the first round of investments back in the early 90's and 2000 do not delivered the promise of the investments made, namely because although the recognized technological potential there were no unmet clinical needs addressed causing some pressure in the demonstration of results under the risk of losing investments proved to be a challenge.

One of the aspects mentioned by stakeholders as a big challenge was the demonstration of significant clinical benefit over the existing therapies, as mentioned in Chapter 3 the cell therapies could present higher manufacturing costs than other existing drugs, the fact that for example in autologous therapies

the achievement of scale economies is not possible also difficult the competition of cell therapies with other treatments, and therefore it is central to being able to provide demonstrations of higher benefits to cell therapies mainly when there are other types of treatments for the same clinical conditions already approved. The process of translation of a product from a research base into an industrial based is other of the biggest challenges faced by the industry, the logistics and requirements associated with the manufacture and clinical trials are still a challenge as well as the achievement of a scalable and robust manufacturing process.

Although the recognized effort of the regulatory bodies to provide adequate regulation and scientific advice to the stakeholders, the regulatory processes still have some challenges, some of them due to the inexperience of the regulatory bodies with this type of technologies The lake of regulation and the possibility of the development of cell therapy products through regulatory exceptions pathways is other of the challenges faced by the industry, this conditions are guilty by increasing the uncertainties and inducing divestment by current investors in Europe. Innovation is other of the mentioned challenges, cell based therapies are innovative products, are new products with different features from the conventional drugs being this novelty also a possible challenge with all the stakeholders and regulatory bodies of the industry currently still learning with the recent discoveries and trying to correct existing fails in the processes involved in the manufacture and commercialization.

The challenges appointed by the academia are mainly related to the lack of knowledge about the potential of the biological product and the mechanisms of action of the therapy. The behavior of the cell based product after the administration is still not fully understand and the complete understanding of this mechanism of action is a challenge. The investment in this industry is also a challenge revealed by the academia, who highlights the fact that the cell therapy industry didn't gathered the complete interest of the major pharmaceutical industry. The lack of personal with formation and experience to deal with the unique features of the cell therapies is also a reason listed.

The next table synthetize the main challenges faced by the Industry in the view of industry members and academia (Table 2).

Summary Table: Main challenges of the cell therapy industry	
Industry	• Innovation and Investments; • The translation process from a research base into an industrial base; • Manufacturing challenges (eg. Scale up); • Demonstration of significant clinical benefit; • Logistics and Regulatory processes for clinical trials; • Lack of regulation and the issue of regulatory exemptions which are causes of divestment.

Academy	• Lack of trained personnel to deal with products which features differ substantially from a conventional drug; • Lack of knowledge about the full action and potential of the biological part of the cell based product; • The interest and consequent investment of the major pharmaceutical industry has not be completely caught yet.

Table 2 Main Challenge of the cell therapy industry

The next conceptual map present aims to provide a global overview of the relations of influence in the challenges context found during this investigation (Figure 20).

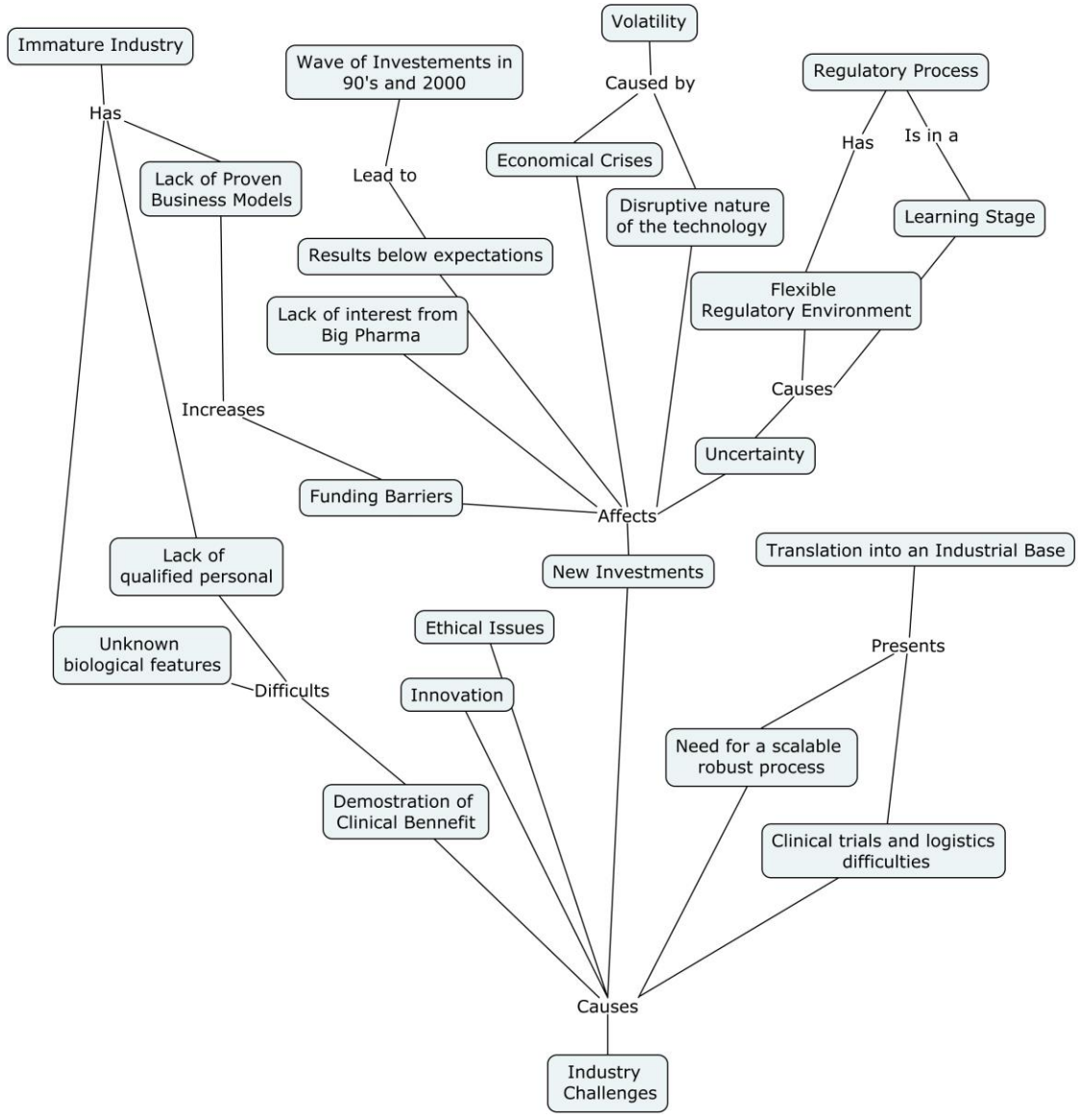

Figure 20 Schematic representation of influences related to the challenges faced by the cell therapy industry

5.2. Constrains to the commercialization of new cell therapies

As happened before, when asked about the main constrains to the commercialization of new cell based therapies one of the main highlighted ideas from the industry stakeholders was the fact that the ratio between healthcare system costs and the value created to patients is high, which is due the high manufacturing costs and difficulties in show significant benefit over conventional therapies, small molecules and other biologics, as mentioned in the previous section. The inexperience in the commercial scale manufacture is other constrain found, as well as the absence of hurly stage venture capital that allow the support and commercialization of new technologies.

The creation of the pricing and reimbursement dossier is also mentioned as an arduous task, this dossier is considered a major undertaken to some cell therapy companies, which difficult the approval of the therapies and consequently avoids commercialization. It is important to have in mind that a considerable percentage of the cell therapy companies are small and have limited human and financial resources once as it was said before the interest of most of the big pharma companies have not been captured yet, which is a constrain cited by both, the Industry and academia.

The next table synthetize the main constrains pointed by the Industry members and academia (Table 3).

Summary Table: Main Constrains to the commercialization of new cell based therapies	
Industry	• Ratio between healthcare system costs and value created to the patients is high; • Create the pricing and reimbursement dossier is an arduous task; • Limited resources; • Inexperience in commercial scale manufacture; • Absence of hurly stage venture capital.
Academy	• The industry is still capturing the interest of big pharma.

Table 3 Main constrains to the commercialization of new cell based therapies

The next conceptual map present aims to provide a global overview of the relations of influence in the Constrains to Commercialization context found during this investigation (Figure 21).

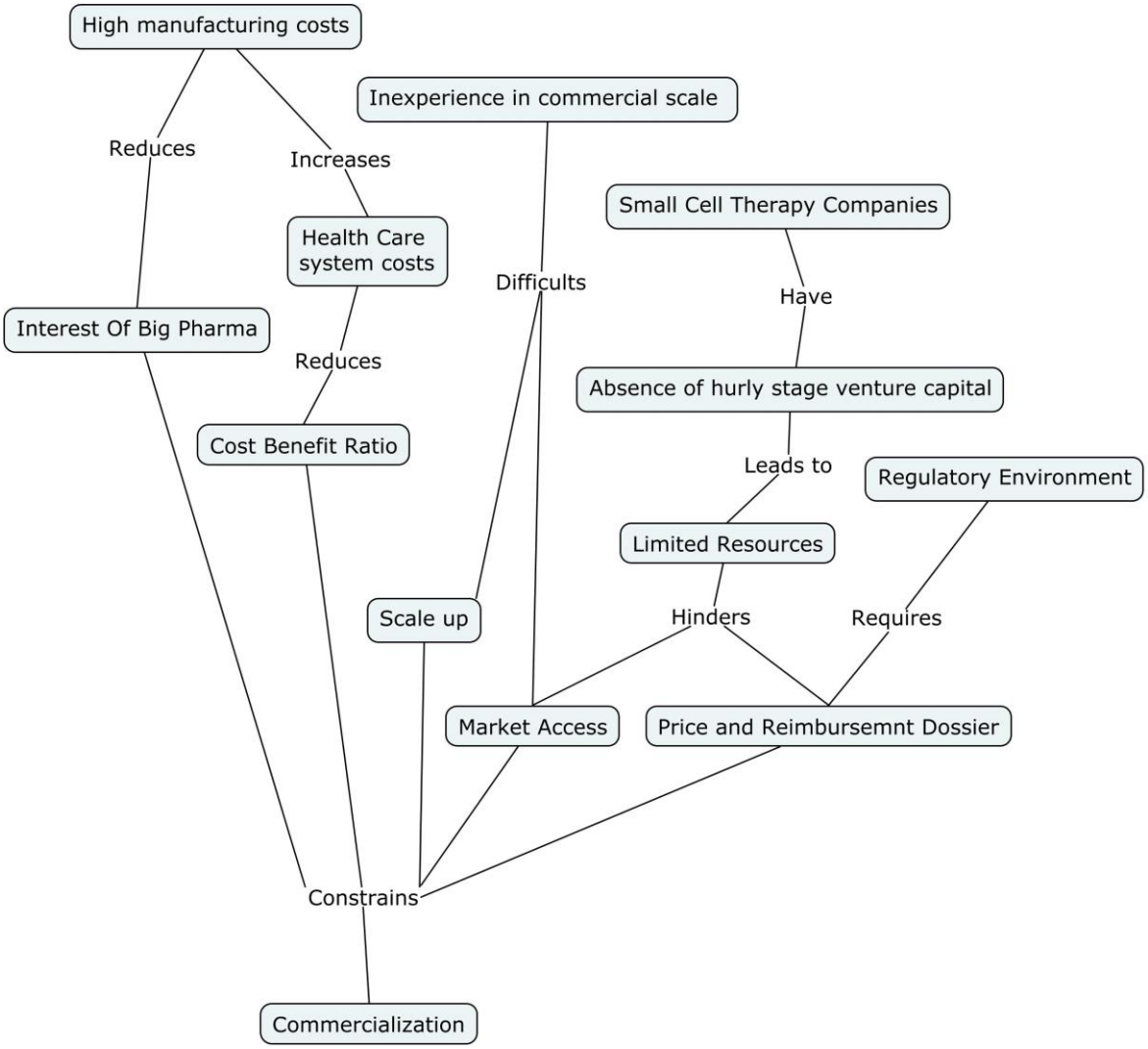

Figure 21 Schematic representation of influences related to the constrains to commercialization

5.3. Reasons for the low number of approved products

A number of products reaching the market inferior to the number of products that are in testing phases is a phenomena common to cell therapies and other biopharmaceutical and conventional drugs in general, what happens is that the cell therapies present additional difficulties due to a set of elements.

The fact that cell therapy is still a recent field is pointed by both, industry and academy as one of the reasons why the amount of products that reaches the markets is so inferior to the number of products in testing phases. Once the industry is still recent, the majority of the development of the cell therapy is still in phase 2 of the research (as is possible to certify with the data from Chapter 3), being hoped a boom as the industry is becoming more mature. The technologies of this industry are innovative

facing the same challenges and distrust already exceeded before by other biologicals, whose industries are already in more mature stages. This technologies are also not completely understood, which increases the challenges in the development of new therapies. The lack of knowledge related to the mechanisms of action leads to the need to maintain a large number of products in development phases before aiming the commercialization. The unknown about the cell therapy products and the mechanisms of action, make it difficult to define exactly the target of the therapy and the effects of a therapy, also leading to the retention of products in research.

The very demanding regulatory environment that supports the industry mainly in the United States and the extensive requirements required for the conduction of clinical trials are other of the reasons mentioned by members of the industry and academics for the low number of products that reaches commercialization. The logistic processes related to the clinical processes, costs involved and technical difficulties that have not been overcome yet, namely with the need to scale up processes and storage of these products also have influence in the success or fail of a product in the testing phases. The next table synthetize the main reasons pointed by the Industry members and academia that led to a low number of approved products (Table 4).

Summary Table: The main reason why the number of products reaching the market is so inferior to the number of products that are in testing phases?	
Industry	• The Industry is still recent; • Manufacturing and healthcare system costs are high; • Mechanisms of action of the cell based products are not fully understood; • Very demanding regulation associated to challenges about macro systems, manufacturing and clinical trials.
Academy	• Lack of information about the cell products in study and the mechanisms of action are not fully understood; • Very demanding regulation; • The Industry is still recent.

Table 4 Reasons for a low number of approved cell-based products

5.4. Influence of regulatory exceptions in the development of the markets and impact of regulation

The importance of the hospital exemptions from the patient's point of view is recognized by all the people of both sectors interviewed. It is very important to patients to have access to alternatives, in the hospital setting from the physician and practice points of view is important to provide access to

the innovation to patients even if that innovation is not completely confirmed, as is the case of hospital exemption products once hospital exemption products result from a patient friendly regulation, specific in an individual member state that aims to provide therapeutic alternatives to treat individual patients with products that have not necessarily gone to the entire process that generates evidence (more about hospital exemption in Chapter 4).

The hospital exemption is also considered a very useful tool that allows that in a European context the academic centers, together with local hospitals to be able to provide added value to patients with their researches, not routine product but individual patients.

The preservation of the hospital exemption in defended and the benefits recognized in certain circumstances for individual patients in individual countries with products in early stages of not confirmed evidence. The question raised is about the scales on which the exemption is used, with the industry members defending that to have a broad approach the process used should be followed the traditional process of clinical development and generation of evidence and the regulatory process that gives extensive approval to multiple countries and member states. The use of hospital exemption in an industrial stage is criticized and considered detrimental to the cell therapy products.

Regulatory exceptions like hospital exemptions are said to have a huge impact on products already in markets (See the case of ChondroCelect in the section Case study 5.8). One of the mentioned problems that creates huge impacts in the markets is the possibility of a companies that have fulfilled all the regular development pathway, that reached the market and that have a market authorization could have their products copied in several countries by multiple hospitals due to the hospital exemption setting. This possibility will lead to the necessity of alterations in the value chain of the product in cause, because if the hospitals (who are the consumers of the cell therapy products, and consequently the patients who are the end consumers) are served internally, manufacturing products that cover their demand, the cell therapy companies will not penetrate in the markets that are supposed causing changes in the distribution channels defined and in target populations. The uncertainties created leads to a lake of investment and that creates an impact in the cell therapy markets that is inclusive expressed by difficulty of sponsor clinical trials.

The current challenge identified is to establish a frontier to the utilization of the hospital exemption setting when there are already approved products in the markets. Not allowing the competition of these approved products with academic sites or hospitals is the main goal once the costs of the products from both settings are not comparable, an advanced therapy medicinal product approved by the regular pathways will always have higher costs in development and compliance with regulatory requirements that will not allow a far competition, because at the end, what happen is a competition for the same markets with products developed with different regulatory criteria . The next table synthetize the main ways how regulatory exceptions, such as hospital exemption, influence the

development of the market of cell therapies in the opinion of cell therapy industry members and academia (Table 5).

Summary Table: How do regulatory exceptions, such as Hospital exemptions, influence the development of the market of cell therapies?	
Industry	• Adds uncertainty to markets; • Potentiates copy of approved therapies; • Competition for the same markets with different regulatory criteria; • Enables patients to access innovation.
Academy	• Allow academic centers in conjunction with local hospitals, to provide added value to research; • Adds potential for patients.

Table 5 Influence of regulatory exceptions as hospital exemption in the development of the markets

It is emphasized by the interviewed that the regulatory process supporting the development of one product from the hospital exemption setting is different from the regulatory process that regulates a product from an industrial setting. An opinion shared by both, industry and academy members is that the hospital exemption setting could facilitate and abbreviate the arrival of cell-based products to the phase of administration in the patient. The fact that a hospital exemption product is used when the generation of evidence is still in progress helps to hurry the process. Due to the aims of the hospital exemption setting the target is not the profits or the routine production but instead provide an available therapeutic alternative to a single patient, unlike the traditional regulatory process which is potential longer and hard but that allows the creation of greater value.

Some cell therapy industry members believe that it could facilitate hospitals and academics to go until the end of the process and that the existence of that possibility does not facilitate the process required to the cell therapy developed by the regular pathways. Figure 22 shows a schematic representation of influences of hospital exemption in the cell therapy markets

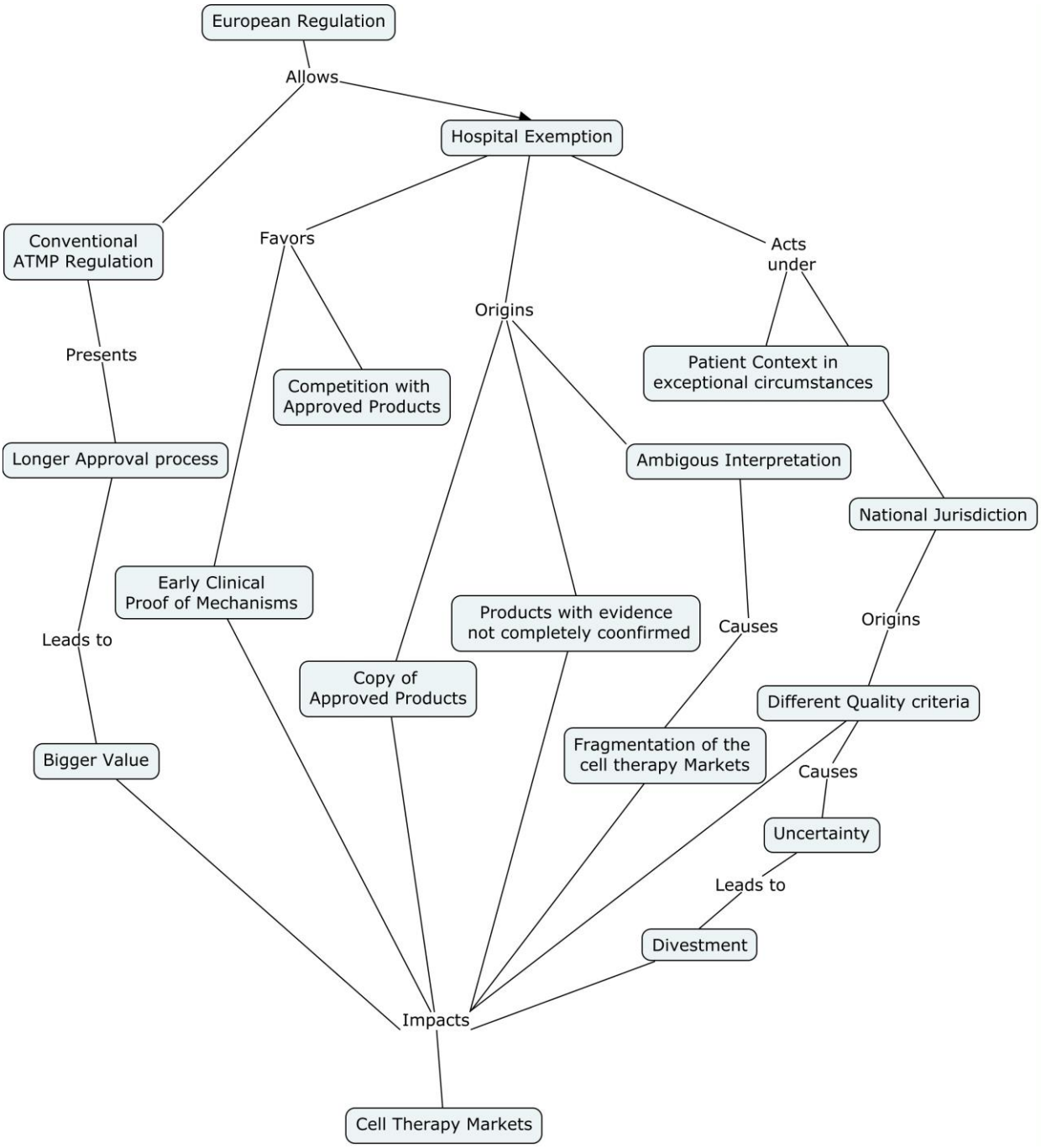

Figure 22 Schematic representation of influences of hospital exemption in the cell therapy markets

The next table synthetize the opinions and points of view about the possibility of the current regulation favor the development of hospital exemption products of the industry and academy members interviewed (Table 6).

Summary Table: Does the existent regulation favor the development of hospital exemption instead of regular products for the same diseases?

Industry	• Favor early clinical proof of mechanisms; • Can facilitate hospitals and academics to go all the way through the end consumer; • Does not help the development of non-hospital exempted products; • The traditional regulatory process is potentially more hard and longer but will lead to a bigger value.
Academia	• Hospital exemption could speed up the arrival of the technology to the phase of administration in the patient ;

Table 6 Possibility of favoritism by the existent regulation

5.5. Uncertainty associated to Hospital Exemption

As we have seen the uncertainty associated to the hospital exemption directly impacts the products already in the markets and in development that were regulated through the regular approval pathways. In order to prevent that the existing uncertainty jeopardize the development and successful commercialization of its therapies the cell therapy companies constantly develop a set of activities to try to protect its products.

One of the strategies presented by the stakeholders was showing the users, the payers and the physicians the evidence documented through the approval mechanism and the benefits of the value created in the development process. The companies use the level of documentation obtained to try to demonstrate and convince the users of the differences between a localized and individual process and an industrial and systematic manufacturing process. The assurance of safety and efficacy documented though the complex regulatory process is used to convince the users of the value created by the therapy. The information mentioned before is also used to try to limit the large use of hospital exemption, is not only the direct comparison between products that is desired but also the assurance that the end consumer understands the value from an industrial manufacturing process.

Companies also try to show to the authorities the implications of the availability of a product from hospital exemption and lobby to change regulation so that the products on the market are not affected by the existence of medical exemption. Trying to move into allogeneic products which are more difficult to be used by this type of regulatory exceptions is other of the ways used by the industry to protect their products and businesses. The next table synthetize the main strategies used by the cell therapy companies In order to protect their products from uncertainty (Table 7).

Summary Table: How does the industry deals with the uncertainty associated with Hospital exemption and tries to protect its products?

Industry	• Lobby within the EC and change regulation; • Showing the users and payers that there is a difference in both products; • Showing the users and payers that an industrial product development brings safety; • Moving into allogeneic development which are more difficult to include in the hospital exemption;

Table 7 Strategies used by the cell therapy companies in order to protect their products

5.6. Establishment of the value chains for cell therapies and the importance of the regulatory framework in this context

In some industry member's opinion the value of cell therapies has been recognized. The investors are satisfied with the increasing believe of the markets in these products and the regulators also detected scientific value, which is proven by the efforts of the regulatory bodies in providing suitable regulation. As mentioned before not only small companies and startups are investing in this field but also companies capable of major investments are starting to see value in this products, as is the case of major pharmaceutical companies like Novartis or Pfizer. Concerning medical doctors, although they are starting to see value, mainly the ones who are in some way related to investigation, some of them could still a bit reticent due the fact they haven't seen much clinical deliverables and the practice is still not very common or broad. The need to be careful and not ruin expectations is other of the points emphasized because it could affect the value seen by the consumers and consequently the investments in this area.

The lake of precedence and predictability are two of the reasons highlighted by industry members as difficulties in the establishment of value chains. There are only very few cases of therapies that already achieved the commercialization phase and the end consumer and therefore there are not enough examples that allow the validation of any theories. The inexperience and unfamiliarity associated with these new technologies leads a continuous learning process as the progression in the value chain is ongoing, thus, the some hurdles are yet being identified by the cell therapy companies.

Technological constrains are other of the reasons pointed by the stakeholders whom remember that in most cases there are not available of the shelf products and the limited shelf life of this type of products creates difficulties, mainly in the distribution process once it imposes the necessity of very fast delivery systems, requiring very controlled settings and timeframes which carries some challenges and impacts the flow of the cell therapy products. Once again, the high costs associated with the manufacturing the distribution costs and the business models are considered hurdles once

the reimbursement will be dependent of this costs. Therefore, the price of the product should be high enough to cover all the manufacturing costs leading to the choice of clinical indications where the high value of the product is recognized and it is possible to establish high prices, namely clinical conditions with no other therapeutic options.

The next table synthetize the main difficulties felt by the industry members related to the establishment of value chains for cell therapy products (Table 8).

Summary Table: Main Difficulties in the establishment of the value chains for cell therapies	
Industry	• Technological constrains; • Lack of precedence and predictability; • Business models and manufacturing costs; • Approval and Reimbursement; • Clinical products flow;

Table 8 Main Difficulties in the establishment of the value chains for the cell therapy products

When asked about the importance of the regulatory framework in the establishment of value chains for the cell therapy industry the opinion is unanimous with all the industry members considering that the regulatory framework carries a very high influence. The regulatory processes are considered essential being desired a regulatory that takes enough risk, therefore it is crucial a strategy in the development of new approaches.

The existing rules and regulation will control the possibilities of success of a product. Owing to limited resources, the developers take important decisions for their products based on a specific regulatory context and so it is fundamental for them to understand what are the rules and how they are going to be applied, consequently it is indispensable to have a clear regulatory environment without changes that could ruin all the investments made for a specific cell therapy company. The hospital exemption is one of the examples of the impact of the regulatory framework in the cell therapy markets.

5.6.1. Value chains: ATMP versus Hospital exemption

The interviewed believe that the value chains of both, hospital exemption products and therapies approved by the regular pathways are different. Figure 23 shows the influences in the cell therapy value chains establishment. In a Hospital exemption setting the value must be considered for the single patient while in an industrial approach there is evidence generated so the value is created to multiple patients or large populations leading to innovation. It is also important to have in mind that for hospital exemption products there is no significant commercial return or confirmed benefits contrary to what happens with an industrial approach which allows a widespread use.

A hospital exemption allows an early access to the markets and the final consumer. Achieving the clinical environment rapidly the product has a faster evolution what also permits that the development team receives constant clinical feedback about the performance of the product, and potential for product flow which will influence by accelerating the overall development and will impact the value chain. The requirements concerning quality control and quality assessment also differ between both types of products and related costs of this tests will impact value chains.

The fact that Hospital exemptions present geographical constraints because they can only be provided within a hospital or country also results in differences in the value chains. Different geographical challenges are also faced by both types of products depending on the country in which they are being applied, once the rules are established in a national jurisdiction and therefore the national regulatory agencies are the ones who will set up the rules to operate internally about hospital exemption. Thus some countries will have more tight guidelines to operate as a regulatory exception then other which will also impact the value chains. For the reasons stated before the hospital exemptions will not have to export between countries avoiding distribution challenges once the manufacturing site in the case of the Hospital exemptions are directly associated to the administration sites (hospitals).

The next table synthetize the main differences stated by cell therapy industry members and academia (Table 9).

Summary Table: What are the main differences between the value chains of regulatory exceptions, namely, hospital exemptions and regular approved products?	
Industry	<u>In the hospital exemption setting:</u> • An early access to treatment means a more rapid evolution of the potential of the product and clinical feedback on product accelerating the development; • There are different geographical constraints; • What is done in quality control and quality assurance is different from the industrial setting.

Table 9 Differences between the value chains of regulatory exceptions, namely, hospital exemptions and regular approved products

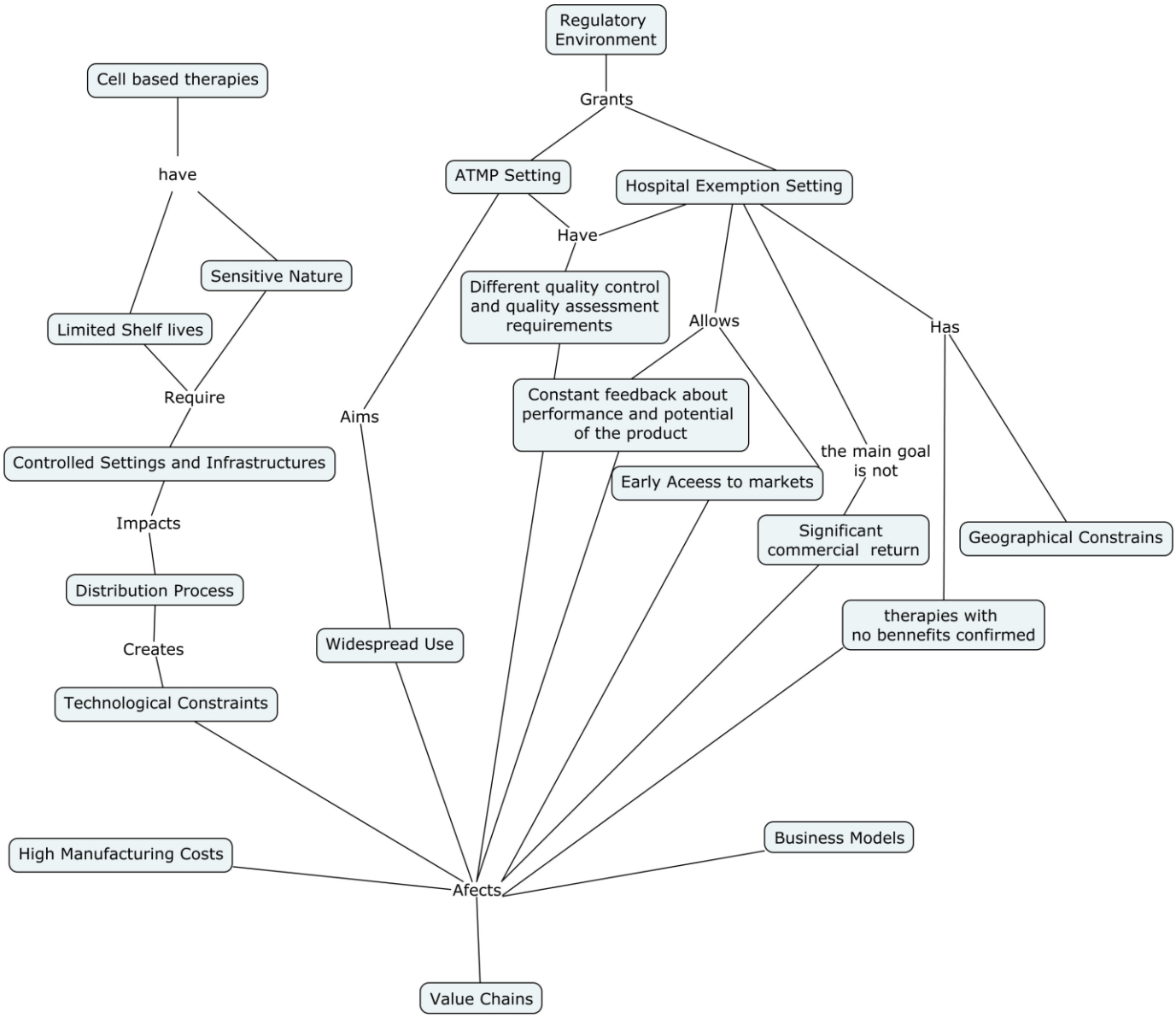

Figure 23 Major influences in the establishment of value chains in the cell therapy industry.

5.7. Differences between the regulatory aspects of the United States and Europe

Despite the fact that there are cultural differences that lead to different regulatory approaches according to the different geographical regions, it is clear to the interviewed that the regulatory agencies responsible, namely, Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have been made an effort to homogenize regulations regardless of geographic location and for scientific terms there is less and less differences. It is also recognized by the industry

members the efforts of both agencies to modernize and adapt to the needs and requirements of the complex nature of the cell therapy products once until recent times these agencies are only dedicated to regulation of conventional pharmaceutical products and therefore the requirements and approval routes shall be adjusted in order to meet the specifications of these innovative technologies, or the requirements would be impossible to fulfill because of the existing differences between both types of products. Despite the recognition in homogenizing policies, the existing differences between regulatory agencies also could lead to the need for adaptation of companies, which in the case of small companies of cellular therapies may prove to be a challenge due to absence of enough financial or human resources.

It is also an opinion shared by members of the industry and members of academia that the regulatory agency responsible for acting in the US, FDA, as a more stringent role in regulation. The requirements required by FDA related to the conduction of clinical and pre-clinical tests are considered tighter and less subjected to risk when comparing with the European Agency, and therefore the approval process in Europe could occur more rapidly.

Despite in Europe the agency responsible for regulating cell therapies being EMA, the territory is fragmented and each country maintains is own regulatory agency which allows the existence of issues of national jurisdiction as is the case of the hospital exemption and consequently the possibility of multiple interpretations of the directives, which could be prejudicial and responsible to fragment the cell therapy markets. This fact also could lead to install an environment of uncertainty due to the multiple possibilities of interpretation of some directives and therefore lead to a destabilization of markets and divestment, being a current challenge of the industry as previously mentioned. On the other hand in US do not exist regulatory exceptions such as hospital exemptions or les specials scheme. Unlike some European cell therapy companies, the North American companies are seen as not being moving in the direction of exceptions as the ones mentioned before or companionate use as parte as their regulatory strategy. The detailed information about the differences of the EU and EUA markets are present in chapter 4.

The approval paths are believed to be changing, evolving to allow more accelerated approval and innovation processes, being once again recognized the efforts made by the European agency in this regard, namely trough regulatory exceptions but also mentioned other adapting accelerated approval paths (an analysis could be consulted in chapter 3 and 4). The next table synthetize the main differences between both regulatory agencies e possible impacts pointed by the Industry members and academia.

Summary Table: How do you compare the regulatory aspects of US and EU, and how their differences influence the cell therapy markets?	
Industry	• Both FDA and EMA are trying to modernize;

	• FDA is more stringent and less subjected to risk; • Europe is in an adaptive pathway; • For scientific terms there less and less differences
Academy	• The American regulatory agency is possibly more stringent; • In Europe the start of a new product could occur faster; • In Europe the fragmentation resulting from specifics of each country could be prejudicial.

Table 10 Differences between the regulatory aspects of the United States and Europe

5.8. Case study

The commercialization of ChondroCelect® and the impact of Hospital Exemption in its market was the selected case study. The reasons for the selection of this case study included the fact that ChondroCelect® was the first approved cell based therapy in Europe, is currently in commercialization in several European but also in countries from other continents and has a set of competitors It has a set of competitors which comprises products from the hospital exemption schema, facts for which there are already some evidence, allowing to build on existing research. ChondroCelect also had been approved for reimbursement in several countries allowing to access the difficulties of this process.

5.8.1. TiGenix

TiGenix is a biopharmaceutical company listed in Euronext Brussels, based in Leuven, Belgium and that has operations in Madrid, Spain. Was founded in 2000 in Leuven, as a spin-off of the Catholic University of Leuven and the University of Ghent and is focused in the development and commercialization of cell therapy treatments, having as main targets autoimmune and inflammatory conditions[83].

TiGenix was responsible for the development and commercialization of the first approved cell-based therapy in Europe, ChondroCelect®. Also had established an advanced clinical stage pipeline based on a validated platform of allogeneic expanded adipose-derived stem cell (eASCs). Is currently developing CX601 a therapy in Phase III of the clinical trials to be applied to patients that suffer from Crohn's disease with complex perianal fistulas, having established an agreement with Lonza for its production in United States and CX611, an allogeneic therapy for the treatment of rheumatoid arthritis that already concluded phase IIa of clinical trials. In 2015 Coretharapix, the company responsible for AlloCSC-01 was acquired by TiGenix. AlloCSC-01 is a cell based therapy currently in phase II of trials to be used in acute myocardial infarction[84]. In Figure 24 is possible to observe a complete list of the products developed by TiGenix, the current clinical trials phase and the indications.

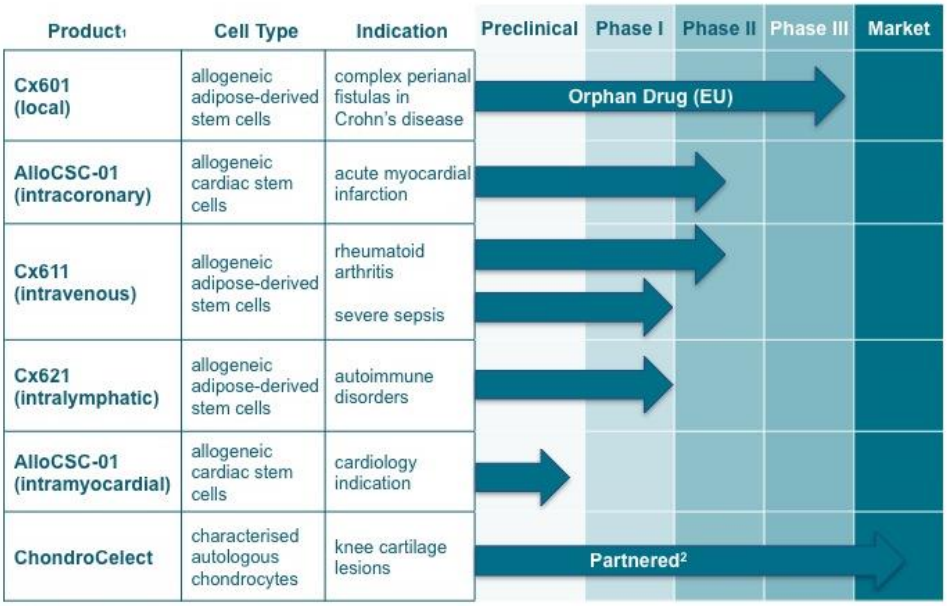

Figure 24 Tigenix 's products development and pipeline by Cell Type and Indication (Souce .Tigenix website)[84]

5.8.2. ChondroCelect®

ChondroCelect® was the first cell-based therapy to receive a European Marketing Authorization in October 2009, being the first Advanced Therapy medicinal product approved by The Committee for Medicinal Products for Human Use. During the clinical trials process, ChondroCelect® has demonstrated to be effective in the treatment of patients with cartilage defects with between 1 and 5 cm^2 in size and has presented an acceptable safety profile according to the assessment implemented by the Committee for Advanced Therapies[85]**.** Currently already has been approved for reimbursement in Belgium (in 2011), Netherlands (in 2012) and Spain (in 2013). In 2014 Tigenix announced that licenses the exclusive marketing and distribution rights for ChondroCelect to Sobi (Swedish Orphan Biovitrum AB) an international healthcare company, the exception if Finland where Tigenx already was an agreement with Finnish Red Cross Blood Services[86]. In US FDA requested additional studies before provide a Biologic License Application (BLA).

5.8.3. Cell therapy and Market

The therapy consisting in autologous chondrocyte implantation aims the regeneration of the hyaline cartilage defects allowing to recover the correct functioning of the joint and is performed in two main steps[87]. The first phase of the treatment includes the collection of cartilage cells from the patient's own knee (arthroscopically). After the collection, the chondrocytes present in the sample are isolated and then expanded in vitro. Nine weeks later, the final product can be re-implanted in the patient's

knee by surgery, repairing the lesions in the knee, through the production of new cartilage by the implanted cells[88].

ChondroCelect® is a cell based therapy prepared individually for each patient, obtained only by medical prescription, indicated to be used for the repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society grades III or IV) in adults[88]. Widuchowaki *et al* showed in the study "Articular cartilage defects: Study of 25.1234 Knee arthroscopies" that 60% of the patients analyzed exhibited Chondral lesions, considering that this type of lesions are common in the knee joint. In total, only 9% of the studied patients showed grade III and IV cartilage lesions[89], the type of lesions where ChondroCelect is indicated to be applied.

The market where ChondroCelect competes is highly fragmented presenting several types of treatments for this pathology. Surgical treatments as debridement, microfracture and mosaicplasty. A study performed in order to assess the cost utility of this cell-based therapy to treat symptomatic knee cartilage lesions in Belgium showed an incremental cost per *quality adjusted life year* of €16 229 and a gain of 1.282 *quality adjusted life years* when compared with other applied surgical treatments (in this specific case comparing with surgical procedure microfracture)[87]. Cell based therapies and cell-free products as scaffolds and gels also are included in the range of competitors of Chondrocelect. MACI from Genzyme is the other cell based product approved by EMA in 2013 for the same conditions, however, *Tetec*, *Co.don* and *Cellmatrix* are other cell therapy companies trying to get EMA approval for its products for the same conditions. Also in Europe, the Hospital Exemption regulation allows the production autologous cartilage by several hospitals for their patients.

5.8.4. Commercialization Challenges

Even being an autologous therapy and therefore where customers are the most important suppliers of raw materials minimizing possible challenges with suppliers, ChondroCelect still presents some challenges related to its commercialization. In the interview performed to Eduardo Bravo Managing Director and Chief Executive Officer of Tigenix one of the main difficulties experienced by ChondroCelect pointed was the size of the market, considered small, with a low number of patients. Being an allogeneic cell based product has as consequences the high manufacturing and distribution costs that will be reflected in a price that can be perceived as high, these circumstances also present a difficulty faced by Tigenix in the commercialization of ChondroCelect and are directly associated with reimbursement issues. The reimbursement dossier prepared was considered a major undertaken and the one clinical trial with positive data and results was not enough some countries which didn't approve the reimbursement of the product, making the market in which ChondroCelect operates even smaller and the manufacturing costs even higher.

The impact of regulatory exceptions as the *Hospital exemption* criteria is considered as huge by the CEO of the company who highlights Germany as an example of a country where are few local companies allowed to stay on the market based on these hospital exemption that sell their own cell therapy products to be applied as cartilage repair products without prove of clinical evidence and with commercialization prices that are inferior to the ChondroCelect manufacturing costs. This lower costs are possible due to the existence of double quality criteria and different quality assessment requirements between the approved therapy commercialized and the products from hospital exemption that have no commercialization restrictions even after ChondroCelect approval.

6. Conclusions

The cell therapy is still in recent stage compared with other fields of the regenerative medicine and there are a set of challenges identified by the cell therapy industry members that must be overcome for the industry to reach its maximum potential. The demonstration of significant clinical benefit over existing therapies is still an issue and some other hurdles identified by the industry members are highly affecting the creation of value in this sector by directly impacting the products' value chains. Investments, regulation and the translation process are major impacting areas currently associated to majority of the barriers described in the previous sections and the need for a scalable and robust manufacturing process is still a challenge. The inexperience associated to the different members responsible for the development and commercialization of the cell therapies, including the regulatory bodies still has repercussions in the success of commercialization of cell based products. The lake of clarification in the regulation of cell therapy products developed through regulatory exceptions is also increasing uncertainties and consequently jeopardizing new investments in this field.

Although the importance of the hospital exemption setting is recognized, its use in direct competition with other cell therapy products approved out of the exemption schemes is criticized and the consequences in the commercialization of this cell based therapies are proven and have impacts in the value chain of these products, namely through the alteration of the market size of the products previously developed and the fragmentation of cell therapy markets. The commercialization of Chondrocelect and the influences felt due to the existence of the regulatory exemptions illustrates the impact of the coexistence of both types of products, the negative effects of the competition and the need to restrain the commercialization of products from the exemption setting after the approval of cell therapy products from the regular setting. Currently in Europe there are several hospitals producing autologous cartilage for their patients under different requirements as the requested Tigenix to produce Chondrocelect.

The differences between the regulatory aspects of the Unites States and Europe influence the cell therapy markets of the different geographical regions. Europe presents a more adaptive pathway for the development of new products while FDA is considered C. Currently, although the standardization efforts by both regulatory agencies, differences are still found. Despite the stringent regulatory environment of in the US, there are no hospital exemption setting allowed by FDA, preventing the competitions of both products in this markets. Cell therapy companies with limited resources could benefit from the standardization of regulations across different geographical areas, sparing resources.

As this study didn't include opinions or information collected from experts developing or investigating through the hospital exemption setting, some of our results may be consequence of opinion convergence by the selected group of interviewees. The present analysis would benefit from the

collection of views from experts involved in hospital exemptions, as they might allow the reader to understand the points of view of all the different intervenient in the field. An analyses of data collected from these stakeholders would be the next step of study, as well as investigate the availability and requirements for new or existent infrastructures and qualified staff (including specialized doctors and nurses) in hospitals, for implementing and producing cell therapy products under hospital exemption legislations would be the next step, followed by an analysis of the economic impact generated.

In addition, this analysis would benefit from the inclusion of patients as a group in the interviewees, as more personalised medical approaches will depend very much on the patients' choices and the growing tendency for patients to engage in the medical decision making processes.

7. References

1. Prescott, C. D. *The delivery of regenerative medicines and their impact on healthcare*. (2011).
2. Atala, A. & Allickson, J. G. *Translational Regenerative Medicine*. (Elsevier, 2014).
3. European biopharmaceutical Enterprises & Transformation, V. Europe ' s Emerging Science Putting Advanced Therapies into Practice to Deliver Better Health. (2015).
4. Mason, C., Brindley, D. a, Culme-Seymour, E. J. & Davie, N. L. Cell therapy industry: billion dollar global business with unlimited potential. *Regen. Med.* **6,** 265–272 (2011).
5. Smith, D. M. Successful Business Models for Cell-Based Therapies. *World Stem Cell Rep. 2008* 158–162 (2008).
6. Research, R. M. PR Newswire. *Stem Cell Therapy Market Growing at 39.5% CAGR, Worldwide to 2020* (2014).
7. European biopharmaceutical Enterprises. EBE position paper on the Hospital Exemption. 2011–2013 (2011).
8. Mednous. An Introduction to the European Regulatory Pathway for Advanced Therapy Medicinal Products. *The ATMP Report* (2015).
9. ADVANCED THERAPIES : WHERE ARE WE NOW ? *Regulatory Rapporteur* (2013).
10. George, B. Regulations and guidelines governing stem cell based products: Clinical considerations. *Perspect. Clin. Res.* (2011).
11. Blackstone, A. in *Sociological Inquiry Principles: Qualitative and Quantitative Methods* **1.0,** 1–29 (2012).
12. Schell, C. The Value of the Case Study as a Research Strategy. *Design* 15 (1992).
13. Baxter, P., Susan Jack & Jack, S. Qualitative Case Study Methodology: Study Design and Implementation for Novice Researchers. *Qual. Rep. Vol.* **13,** 544–559 (2008).
14. Daley, B. J. & Milwaukee, W. *Using Concept Maps in Qualitative Research*. (2004).
15. Brightman, J. Mapping methods for qualitative data structuring (QDS). *IOE Conf.* 1–14 (2003).

16. Daley, G. Q. & Scadden, D. T. Prospects for Stem Cell-Based Therapy. *Cell* **132,** 544–548 (2008).

17. Liras, A. Future research and therapeutic applications of human stem cells: general, regulatory, and bioethical aspects. *J. Transl. Med.* **8,** 131 (2010).

18. McGowan Institute for Regenerative Medicine. RegenerativeMedicine.net. *What is regenerative Medicine?* (2010). Available at: http://www.regenerativemedicine.net/What.html. (Accessed: 1st June 2016)

19. Bubela, T. & McCabe, C. Value-engineered translation for regenerative medicine: meeting the needs of health systems. *Stem Cell Dev.* **22,** 89–93 (2013).

20. Hildreth, C. Landmark Events in Stem Cell Development Shift Industry Dynamics [Timeline]. Available at: http://www.bioinformant.com/landmarkevents-in-stem-cell-development-shift-industry-dynamics-timeline/.

21. Kimbrel, E. A. & Lanza, R. Current status of pluripotent stem cells: moving the first therapies to the clinic. *Nat. Rev. Drug Discov.* (2015).

22. Nienow, W., Mccall, M. J., Coopman, K., Kara, B. & Hewitt, C. J. The translation of cell-based therapies : clinical landscape and manufacturing challenges. **10,** 49–64 (2015).

23. Brindley, D. A. *et al.* The impact of market volatility on the cell therapy industry. *Cell Stem Cell* **9,** 397–401 (2011).

24. Mason, C. & Manzotti, E. Regen: the industry responsible for cell-based therapies. *Regen. Med.* **4,** 783–785 (2009).

25. Syed, B. A. & Evans, J. B. Stem cell therapy market. *Nat. Rev. Drug Discov. 12* 185–186

26. McKernan, R., McNeish, J. & Smith, D. Pharma's developing interest in stem cells. *Cell Stem Cell* **6,** 517–520 (2010).

27. Maciulaitis, R., D'Apote, L., Buchanan, A., Pioppo, L. & Schneider, C. K. Clinical development of advanced therapy medicinal products in Europe: evidence that regulators must be proactive. *Mol. Ther.* **20,** 479–82 (2012).

28. Paul- Ehrlich-Institut. *Advanced Therapy Medicinal Products (ATMP)* Available at: http://www.pei.de/EN/medicinal-products/advanced-therapy-medicinal-products-atmp/advanced-therapy-medicinal-products-atmp-node.html. (Accessed: 1st August 2015)

29. U.S. Food and Drug Administration Protecting and Promoting Your Health. *Marketed Products* Available at: http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/. (Accessed: 1st August 2015)

30. Abbott, S., Mackay, G., Durdy, M., Solomon, S. & Zylberberg, C. Twenty years of the International Society for Cellular Therapies: the past, present and future of cellular therapy clinical development. *Cytotherapy* **16,** S112–9 (2014).

31. Barkholt, L., Advice, S., Party, W. & Voltz, C. ATMP Development Challenges – from Scientific Advice to Marketing Authorisation. *Eur. Med. Agency Sci. Med. Heal.*

32. Atala, A. *Progenitor and Stem Cell Technologies and Therapies*. (2012).

33. Kim, I. A brief overview of cell therapy and its product. *J. Korean Assoc. Oral Maxillofac. Surg.* **39,** 201–2 (2013).

34. Coopman, K., Medcalf, N. & Centre, E. From production to patient : challenges and approaches for delivering cell therapies. **44,** 1–11

35. Mason, C. & Manzotti, E. The Translation Cycle: round and round in cycles is the only way forward for regenerative medicine. *Regen. Med.* **5,** 153–155 (2010).

36. Salter, B., Zhou, Y. & Dutta, S. The political economy of the global stem cell therapy market. 1–23

37. Herbert, C. Addressing commercialisation challenges for cell therapies. *CATAPULT CELL THERAPY*

38. Zvonic, S. GEN. *10 Tips for Developing a Successful Cell Therapy* Available at: http://www.genengnews.com/gen-articles/10-tips-for-developing-a-successful-cell-therapy/4447/. (Accessed: 7th August 2015)

39. Egloff, M. & De Viron, G. Cell Therapy Process and Cost Model Simulations. *ATMI White Pap.* **2010,** 1–2 (2011).

40. BERSENEV, A. Stem Cell Assays. *Success of cell therapy producs after approval* (2012). Available at: http://stemcellassays.com/2012/05/success-cell-therapy-producs-approval/. (Accessed: 15th September 2015)

41. Kefalas, P. & Access, M. Assessment of reimbursed price potential for a cell therapy in development of Health Economics & Market Access. (2014).

42. Jørgensen, J., BA & Panos Kefalas. Market Access & Health Policy. *REIMBURSEMENT OF LICENSED CELL AND GENE THERAPIES ACROSS THE MAJOR EUROPEAN HEALTHCARE MARKETS* (2015). Available at: http://www.jmahp.net/index.php/jmahp/article/view/29321.

43. Jorgensen, J. & Kefalas, P. Variations in cell therapy reimbursement across the Big5EU. (2015).

44. Osterwalder, A. & Pigneur, Y. *Business Model Generation: A Handbook for Visionaries, Game Changers, and Challengers*. *A handbook for visionaries, game changers, and challengers* (2010). doi:10.1523/JNEUROSCI.0307-10.2010

45. Chesbrough, H. Business model innovation: Opportunities and barriers. *Long Range Plann.* **43,** 354–363 (2010).

46. Chesbrough, H. & Rosenbloom, R. S. *The role of the business model in capturing value from innovation : evidence from Xerox Corporation ' s technology spin-off companies*. *Industrial and Corporate Change* **11,** (2002).

47. Driscoll, D. Addressing Business Models, Reimbursement, and Cost of Goods. *Bioprocess Int.* **9,** 46–48 (2011).

48. Couto, D. S., Perez-Breva, L. & Cooney, C. L. Regenerative Medicine: Learning from Past Examples. *Tissue Eng. Part A* **18,** 120725085622009 (2012).

49. Foley, L. & Whitaker, M. Concise Review: Cell Therapies: The Route to Widespread

Adoption. *Stem Cells Transl. Med.* **1,** 438–447 (2012).

50. Hourd, P., Chandra, A., Medcalf, N. & Williams, D. J. Regulatory challenges for the manufacture and scale-out of autologous cell therapies. 1–13 doi:10.3824/stembook.1.96.1.1

51. Trainor, N., Pietak, A. & Smith, T. Rethinking clinical delivery of adult stem cell therapies. *Nat. Publ. Gr.* **32,** 729–735 (2014).

52. Technology Strategy Board. Regenerative Medicine : Navigating the Uncertainties VALUE Project Final Report. *Technol. Strateg. Board* 1–73 (2012).

53. Razvi, E., Oosta, P. D. G. & Ph, D. *Stem Cells Market Trends based on Primary Industry Analysis*. (2013).

54. Hourd, P., Ginty, P., Chandra, A. & Williams, D. J. Manufacturing models permitting roll out/scale out of clinically led autologous cell therapies: Regulatory and scientific challenges for comparability. *Cytotherapy* **16,** 1033–1047 (2014).

55. Smith, D. M. Assessing commercial opportunities for autologous and allogeneic cell-based products. **7,** 721–732 (2012).

56. Kaplinsky, R. & Morris, M. A HANDBOOK FOR VALUE CHAIN An Important Health Warning or A Guide for Using this Handbook. *Inst. Dev. Stud. Bright. UK* 4–7 (2000).

57. Christopher Martin. *Supply Chain*. *Communications of the ACM* **48,** (2011).

58. Tait, J. *et al. Business models and value systems for regenerative medicine therapies: rationale and methodology*. *TSB/ESRC Realise Project* (2010).

59. Wolf, J. *The nature of supply chain management research*. (2008).

60. Heber-Katz, E. & Stocum, D. L. in *New Perspectives in Regeneration* (2013).

61. Hamson, B. PCT pulse A Caladrius Company. *Development by Design Principles in Cell Therapy Manufacturing* (2015). Available at: http://www.pctcaladrius.com/pct-pulse/development-by-design-principles-in-cell-therapy-manufacturing. (Accessed: 30th August 2015)

62. Lakelin, M. *Cell Therapy Supply Chain Challenges*.

63. Teng, C. W., Foley, L. & Neill, P. O. *An Analysus of Supply Chain Strategies in the Regenerative Medicine Industry - Imlplications for Future Development*. *Intern. Journal of Production Economics* (Elsevier, 2013). doi:10.1016/j.ijpe.2013.06.006

64. Salter, B., Zhou, Y. & Dutta, S. The political economy of the global stem cell therapy market. 1–23

65. EMA. *What we do* Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42. (Accessed: 15th July 2015)

66. The institute of Medicine, National Academy of sciences & International society for stem cell research. *Stem Cell Therapies Opportunities for ensuring the quality and safety of cilinal offerings*.

67. Chin, W. EUCRAF. *Future approach to development pathways for advanced*

therapy medicinal products (ATMP) Available at: http://www.eucraf.eu/future-approach-to-development-pathways-for-atmp. (Accessed: 5th October 2015)

68. European Medicines Agency. *Advanced-therapy medicinal products* Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0. (Accessed: 7th October 2015)

69. NHS. *Clinical trials and medical research - Phases of trials* Available at: http://www.nhs.uk/conditions/clinical-trials/Pages/Phasesoftrials.aspx. (Accessed: 27th October 2015)

70. Mount, N. *Clinical development of cell based therapies in the UK*. *Catapult* (2013).

71. The European Commission. Detailed guidelines on good clinical practice specific to advanced therapy medicinal products. **10,** (2009).

72. Services, U. S. D. of H. and H. & Food and Drug Administration. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance. in *Trial* (1996).

73. Wilder, P. Van. Advanced therapy medicinal products and exemptions to the Regulation 1394 / 2007 : how confident can we be ? An exploratory analysis. **3,** 1–9 (2012).

74. Hunter, B. European Commission. *Int. J. Integr. Care* **1,** (2001).

75. Medicines Evaluation Board. Public consultation on the regulation on advanced therapy medicinal products - Comments from the national expert group on ATMPs, the Netherlands.

76. Cuende, N. *et al.* The puzzling situation of hospital exemption for advanced therapy medicinal products in Europe and stakeholders' concerns. *Cytotherapy* **16,** 1597–1600 (2014).

77. Martens, M. & Carbonnelle, N. Bird & Bird. *Challenges and perspectives of the regulatory landscape of ATMPs in Europe* (2014). Available at: http://www.twobirds.com/en/news/articles/2014/global/challenges-and-perspectives-of-the-regulatory-landscape-of-atmps-in-europe. (Accessed: 10th November 2015)

78. MHRA Regulating Medicinesand Medical Devices. *The supply of unlicensed medicinal products (' specials ')*. (2014).

79. MHRA Regulating Medicine sand Medical Devices. *Guidance on the UK's Arrangements under the Hospital Exemption Scheme*. **5,** (2010).

80. Gaspar, H. B., Swift, S. & Thrasher, A. J. 'Special Exemptions': Should They Be Put on Trial? *Mol. Ther.* **21,** 261–262 (2013).

81. Benton, K. *US FDA Regulatory Framework for Cellular Therapy Products FDA Mission Statement*. (2013).

82. Deal, G. Stem Cell Therapy Regulations: The US vs the EU. *Regul. Rapp.* **6,** 4–6 (2009).

83. REUTERS. *Tigenix NV(G9U.BR)* (2016). Available at: http://www.reuters.com/finance/stocks/companyProfile?rpc=66&symbol=G9U.BR.

84. TIGENIX. *Company* Available at: http://www.tigenix.com/en/page/4/company.

(Accessed: 8th May 2016)

85. European Medicines Agency. *ChondroCelect* Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000878/human_med_000698.jsp&mid=WC0b01ac058001d124.

86. TiGenix. TiGenix licenses exclusive marketing and distribution rights for ChondroCelect to Sobi. 1–3 (2014).

87. Gerlier, M. L. *et al.* The Cost Utility of Autologous Chondrocytes Implantation Using ChondroCelect® in Symptomatic Knee Cartilage Lesions in Belgium. *Pharmacoeconomics* **28,** 1129–1146 (2012).

88. Tigenix. Tigenix. *ChondroCelect* (2014). Available at: http://www.tigenix.com/en/page/150/chondrocelect. (Accessed: 6th May 2016)

89. Widuchowski, W., Widuchowski, J. & Trzaska, T. Articular cartilage defects: Study of 25,124 knee arthroscopies. *Knee* **14,** 177–182 (2007).

Supplementary Data

Interview Protocol

The set of questions established to function as interview guidelines for the semi-structured interview to be performed to the cell therapy industry players covers the various topics which are intended to be studied. The questions focus the hurdles associated with commercialization of cell therapy products, the establishment of the value chains and the impact hospital exemption products and are presented below.

1- *Could you please make a brief description of your current position and your career experience?*

2- *What do you consider to be the main challenges for the industry of cell therapies?*

3- *What do you believe is the main reason for number of products reaching the market to be so inferior to the number of products that are in testing phases?*

4- *What are the main constrains to the commercialization of new cell therapies?*

5- *Do the establishment of value chains for cell therapies shows difficulties? If yes, what are the main reasons?*

6- *Could you classify the importance of the regulatory framework in this process as low, medium or high? Can you provide examples of this impact?*

7- *What are the main difficulties of changing the value chain of a cell therapy throughout the product life cycle?*

8- *How do regulatory exceptions, such as Hospital exemptions, influence the development of the market cell therapies? Does it have an impact of the products values chain? And does it have an impact on approved products?*

9- *What are the main differences between the value chains of regulatory exceptions, namely, hospital exemptions and regular approved products?*

10- *Does the existent regulation favor the development of hospital exemptions instead of regular products, for the same diseases?*

11- *How does the industry deal with the uncertainty associated with Hospital exemptions? How the industry tries to protect its products from this uncertainty?*

12- *How do you compare the regulatory aspects in the Us and in Europe how do you believe their differences influence the cell therapy markets*

Selection of the participants likely to be interviewed

Before the selection of the participants likely to be interviewed, it was established that the participants should present different backgrounds in order to collect opinions of participants from different fields related to the cell therapy industry, analyzing if the opinions of the participants are dependent on the field in which they are included but also to analyze if it is possible to find patterns in their answers.

The four major fields related to the cell therapy industry desired to be present in this study were: Academia, one of the main responsible areas for promoting the development of cell therapies, being one of the major developer of cell therapies in the initial stages of the research process. Regulatory agencies, namely the European Medicines Agency, one of the bodies responsible for the regulation and supervision of the process of development and commercialization of new cell therapies. Cell therapy companies, corporations that are at the moment involved in processes of development of new cell therapy products or that have already approved cell therapy products in commercialization. Medical Doctors, also responsible for the selection of the best treatment for each patient and for the adoption and application of cell therapies.

The selected fields listed above would allow gathering information and opinions of people involved in the whole process of development and commercialization and application of a new product. After the selection of the fields desired, a web research on the different listed areas was conducted in order to find the possible participants on the interviews, as well as the establishment of contact with possible intermediates to interview people on these fields. The experience and background were the main selection criteria, but the availability of the participants to take part in interviews outlined the dates established had a major influence on the amount of data collected.

After the selection of the desired participants, the contact was established via email. All the stakeholders in the industry of cell therapies selected as likely to be interviewed received an email in which the responsible for the study and the main goals of the project were presented and in which it was asked if the stakeholders are available to participate in the interview process, the context and

propose of the interview were presented and the reasons why their participation was important for the development of the study were also explained on the email.

Identification of the participants

In total ten possible stakeholders were asked to participate in this study. Concerning Regulatory Agencies and regulatory issues, were established three contacts with regulators from different countries (Portugal, Spain and Germany) and consequently different regulatory realities. Regarding academia, only one contact was established with an intervenient exclusively dedicated to the academic field, however, almost all the other stakeholders contacted have connections to the academic area. Relative to Cell therapy companies, five participants, all of them linked to cell therapy companies currently developing new cell therapies, were asked to be part of the conducted study. At last, only one medical doctor, practicing medicine at the time was contacted but one of other stakeholders contacted is also a medical doctor. After the establishment of the contacts it was possible to have six participants, one member of the academia, one member a regulatory agency and four members of cell therapy companies. The remaining experts contacted have declined or not responded to the invitation for participation in the study. A brief presentation of the interviewed is shown below.

Daniela Couto

Daniela Couto has a master degree in Biomedical engineering by University of Minho and a PhD degree in Bioengineering from Lisbon Tech, Technical University of Lisbon in association with Massachusetts Institute of Technology. In 2011 after her graduation, Daniela Couto was one of the co-founders of Cell2b, a start-up of Lisbon Tech and in the same year had been awarded with the Women Entrepreneur Award – Start 2011 by ANJE, the Portuguese Association for Young Entrepreneurs. Currently, Cell2b is a biotechnology company focused in the development of therapies to be applied to patients who suffer from immune, oncological and inflammatory conditions and Daniela was the CEO and Vice-President of the company, being responsible raising money and for the design of the clinical trial studies and clinical development programs, among other responsibilities.

Margarida Menezes Ferreira

Margarida Menezes Ferreira has a PhD by the Université d' Aix-Marseille II -Faculté de Medecine. Currently she has roles as Scientific and Regulatory Advice Coordinator and as Senior Assessor and Member of the National Commission for Medicines Evaluation in INFARMED, National Authority of Medicines and Health Products, (Portugal). She also acts as an Alternate member of the Committee for Advanced Therapies (CAT) and as Senior Quality Assessor in the European Medicines Agency, EMA, (United Kingdom). In Academia, she is a Professor in University of Lisbon - Faculty of Pharmacy

and a Guest Professor in University of Coimbra- Faculty of Pharmacy and Aveiro University - Course on Pharmaceutical Medicine. Her extensive experience in regulatory agencies and with advanced therapy medicinal products in the national and European context was the main reason for the interview.

Cláudia Lobato da Silva

Cláudia Lobato da Silva is graduated in Chemical Engineering by Lisbon Tech, Technical University of Lisbon and has a PhD in Biotechnology by Lisbon Tech, Technical University of Lisbon in association of University of Nevada, Reno, USA.

Currently she is an Assistant Professor in the Department of Bioengineering, Lisbon Tech- University of Lisbon and develops her research mainly about adult stem cells, having interests in the development of cellular therapies and bioreactor strategies for the clinical-scale production. During her research had already established partnerships with local hospitals, namely, Instituto Português de Oncologia, Hospital de Santa Marta and Hospital de Santa Maria

Miguel Forte

Miguel Forte had MD and a PHD in immunology by the Faculty of Medicine and Dentistry of the University of Birmingham. Had practiced clinical medicine in Portugal and in the United Kingdom and was Vice- Chairman of the Portuguese New Drugs Committee within the Portuguese Health Authority in INFARMED, responsibilities that included a role in the European context, having experience in the regulatory affairs department.

Currently, he is the Chief Operating Officer at TxCell a biotechnology company focused in the development of T cell immunotherapies for chronic inflammatory and autoimmune diseases, having responsibilities in project management, clinical development and regulatory affairs. He is also chair of the committee for International Society for Cellular Therapy and is an invited professor at Universidade de Aveiro and Universidade de Lisboa- Faculdade de farmácia. His wide experience with regulatory agencies but also companies developing cell therapy products and with the clinical context were the main reasons for his selection.

Robert Deans

Robert Deans has BSc in molecular biology by Massachusetts Institute of Technology and a PhD in microbiology by the University of Michigan. He is the Executive Vice President of Regenerative Medicine at Athersys, a clinical-stage biotechnology company focused on the development new therapies in the regenerative medicine area. He is also and a chairman of the International Society for Cellular Therapy Commercialization Committee and his wide experience with regenerative

medicine not only in the European context, but also within the United States markets are the main reasons for his selection.

Eduardo Bravo

Eduardo Bravo has a degree in Business Administration and an MBA by INSEAD. Currently he is the CEO of TiGenix, a biotechnology company focused in the development of cell therapies to be used for patients with autoimmune and inflammatory conditions, this company has the first cell based therapy product approved in Europe, ChondroCelect® which is currently in commercialization. He is also the Vice-President of European Biopharmaceutical Enterprises (EBE) and member of the Executive Committee of the Alliance for Regenerative Medicine. His experience with the entrance on the market and commercialization of ChondroCelect® are the main reasons for his selection.

Interview Process

Excepting the interview performed to the member of Academia, Claudia Lobato da Silva which was performed in person, all the interviews were accomplished by the use of the Skype application due to time limitations and geographic location of the participants. All the interviews started by the presentation of the interviewer and of the study, followed by a request to record the audio and take notes during the interviews. The interviews had an average duration time of thirty minutes and the participants were informed that the audio and notes taken during the interview would then be transcribed and analyzed. The interview process lasted from July to September of the year 2015.

Frequency and Distribution of the information collected

In order to understand the main topics mentioned by the interviewers and to understand the distribution and the frequency of the responses presented in the previous sections, the next tables contain some of the topics and points of view collected from the interview responses.

It is important to have in mind that the following data are only a collection of some the considered aspects presented before. These information are main topics addressed in the responses and not a transcriptions of the responses. The number of the interview in the table don't correspond to the order of the participants presented before.

Table 11 Main topics addressed about the main challenges for the industry of cell therapies

What do you consider to be the main challenges for the industry of cell therapies?

Interview 2	• Little is known about the biological part of that product; • Previous expectations resulted in failure; • Lack of trained people; • Need to capture the pharmaceutical industry.
Interview 3	• Challenges varies according geographical locations; • The first waves of investments didn't' deliver the expected results; • Regulatory environment; • Hospital exemptions are not clearly defined among the countries.
Interview 4	• Innovation; • Translation from a research base into an industrial base; • Logistics; • Manufacturing and clinical development; • Regulation for the clinical trials.
Interview 5	• Demonstration of significant clinical benefit • Lots of promises and slow delivery

Table 12 Main topics addressed about the main reason for number of products reaching the market to be so inferior to the number of products that are in testing phases

What do you believe is the main reason for number of products reaching the market to be so inferior to the number of products that are in testing phases?	
Interview 1	• Demanding regulatory agencies; • Lack of information about the products and its potential; • State of the Industry.
Interview 3	• It is a very young field; • A boom of new cell based therapies reaching the market will mean that the field is becoming more mature.
Interview 4	• Manufacturing Challenges; • Clinical Trials Challenges. • A lot of the mechanisms of action are not fully understood; • Industrialization challenges;

Table 13 Main topics addressed about the main difficulties of changing the value chain of a cell therapy throughout the product life cycle

What are the main difficulties of changing the value chain of a cell therapy throughout the product life cycle?	
Interview 1	• To an indication which none therapy works, having a positive value chain and having a sustainable problem should not be a problem for a cell therapy product.
Interview 5	• Process improvement; • Moving to commercial scale manufacturing; • Maintaining product attributes and product potency with the process changes.

Table 14 Main topics addressed about the main differences between the value chains of regulatory exceptions, namely, hospital exemptions and regular approved products

What are the main differences between the value chains of regulatory exceptions, namely, hospital exemptions and regular approved products?	
Interview 3	• The value chains are very different; • In the HE setting the hospital there are geographically constraints; • The geographic focus and challenges of both types of products are completely different; • Quality control and quality assurance is different.
Interview 5	• A HE could represent an earlier access to treatment and rapid evolution of the potential for product flow; • A HE allows providing clinical feedback on product class performance that accelerates overall development.

Table 15 Main topics addressed about the main constrains to the commercialization of new cell therapies

What are the main constrains to the commercialization of new cell therapies?	
Interview 1	• To have a dossier is a major undertaken; • Limited resources; • Working in an environment that was not 100% clear; • Demonstrate significant difference.
Interview 2	• The interest of the big pharma was not captured yet.
Interview 3	• The ration between the value created to a patient and the healthcare system costs; • Manufacturing costs are high comparing with small molecules and other biologics.
Interview 4	• Scale up. • Pricing and reimbursement dossier; • Market access; • Showing the value and how that value compares with the existing proposals.
Interview 5	• Inexperience in commercial scale manufacture; • Absence of hurly stage venture capital.

Table 16 Main topics addressed about the establishment of value chains for cell therapies

Do the establishment of value chains for cell therapies shows difficulties? If yes, what are the main reasons?	
Interview 1	• Approval; • Reimbursement; • The price needs to be high enough to sustain the manufacturing costs.
Interview 3	• Technologic constraints; • Limited shelf lives; • The distribution is very challenging; • Difficult to have of the shelf products due to the limited shelf lives; • Need of a fast delivery system.

Interview 5	• Lack of precedence and the lake of predictability; • Uncertainty; • Business models; • Clinical products flow; • Potency assessment of the clinical product.

Table 17 Main topics addressed about the importance of the regulatory framework in this process

Could you classify the importance of the regulatory framework in this process as low, medium or high? Can you provide examples of this impact?	
Interview 1	• High; • The clear definition of the rules are very important.
Interview 3	• High; • The hospital exemption an example.
Interview 4	• High; • Regulatory is essential and it needs to be a regulatory that takes significant risk but does not take undo risk.
Interview 5	• High.

Table 18 Main topics addressed about how regulatory exceptions, such as Hospital exemptions, influence the development of the market cell therapies

How do regulatory exceptions, such as Hospital exemptions, influence the development of the market cell therapies? Does it have an impact of the products values chain? And does it have an impact on approved products?	
Interview 1	• Huge Impact; • Different quality standards; • Little by little authorities and regulatory are understanding the issue.
Interview 2	• Very interesting initiative; • Allows in the European context that academic centers together with local hospitals can add value to the type of research that is done and therefore with potential for patients.
Interview 3	• Undefinitions create uncertainty and lake of investment; • A company can have is product copied in several countries by several hospitals due HE in their own countries; • Distribution channels will change significantly; • There are clear advantages of using HE ate the early stages; • The challenge is set the frontier after the existence of products approved. • Companies can have its products several hospitals due HE in their own countries.
Interview 4	• It is essential to have the opportunity to access innovation, even if that innovation is not completely confirmed; • The same products being treated through hospital exemption in different countries and even if the product is necessarily different in different sites by slightly processes is not good for the patient for the industrial approaches and for the regulatory consistency;

	• In an industrial scale the use of hospital exemption should no longer be done, and it is actually detrimental to the product.
Interview 5	• Does not sees Hospital exemptions posing a legitimate path to development.
Interview 6	• Nothing prevents the coexistence of the two systems, which is one of the criticisms that has been made.

Table 19 Main topics addressed about if the existent regulation favor the development of hospital exemptions instead of regular products, for the same diseases

Does the existent regulation favor the development of hospital exemptions instead of regular products, for the same diseases?	
Interview 1	• Could not favors, but doesn't help the non-hospital exempted products; • Authorities are looking starting to understand the issues associated; • Could have been used by some companies and hospitals to compete through a different channel with the authorized products.
Interview 2	• The process may be much shortened by the hospital exemption.
Interview 3	• Depends on the technology involved; • HE can facilitate hospitals and academics to go all the way through.
Interview 4	• It is an option for an individual patient in need; • The traditional regulatory process is potentially more challenging longer but will lead to a bigger value.
Interview 5	• Hospital exemptions favor early clinical proof of mechanisms.
Interview 6	• There are few approved ATMPs; • In Portugal there were no submissions for Hospital exemptions to compare.

Table 20 Main topics addressed about how the industry deals with the uncertainty associated with Hospital exemptions

How does the industry deal with the uncertainty associated with Hospital exemptions? How the industry tries to protect its products from this uncertainty?	
Interview 1	• Trying to convince the authorities and trying to show what does it mean to the companies to have this HE available; • Trying to move into allogeneic development wish are more difficult to include in this hospital exemption.
Interview 3	• The industry tries to lobby and change the legislation.
Interview 4	• The companies will try to convince the users of that differences; • It is important to assure that the payer understands the value that an industrial product brings by the safety and the efficacy documented by the extensive regulatory process.
Interview 5	• Tring to exert regulatory pressure on standards.

Table 21 Main topics addressed about regulatory aspects in the US and in Europe and how their differences influence the cell therapy markets

How do you compare the regulatory aspects in the US and in Europe how do you believe their differences influence the cell therapy markets	
Interview 1	• Both, FDA and EMA are trying to start modernize as most as possible the regulation; • Europe is a little bit more in this adaptive pathway and trying to find ways in what the products could be at least partially approved; • FDA tends to be more stringent.
Interview 2	• FDA could be more stringent in the beginning; • Differences in the translations and interpretation of regulation from country to country in Europe; • Europe may be faster to start but is penalized by this fragmentation of rationality.
Interview 3	• Europe has very different steps then the FDA; • For small companies adapting to this different realities is quite a challenge because the lake of resources.
Interview 4	• Differences in terms of the fund steps; • Willingness of the investors in the US are to take the risk versus the European; • Differences in manufacturing requirements; • FDA could be more interactive; • Currently for scientific terms there is less and less differences; • The biggest difference is probably in cover some risk and the aggressiveness of the culture in the US which translates in the regulatory as well as in other practices versus the European.
Interview 5	• Differences in the compassionated use or differences in use of the hospital exemptions; • Very few Norte American companies move in the direction of the hospital exemptions or companionate use as parte as their regulatory strategy.