Value creation in the cell therapy industry
The role of regulation

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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 expenses1,2. 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 expectations3,4.*
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 cell therapy products through the Hospital exemption scheme has negative impacts in the commercialization of other cell based products.

Keywords — Cell therapy; regenerative medicine; hospital exemption; value creation; regulation.

I. 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 explore and systematize the main problems related to the creation of value in this specific industry and the relations between them, based on data collected along different stakeholders of the industry. The current hurdles associated to the establishment of value chains, the impact of regulation, namely trough hospital exemption setting and the differences between United States and European legislation were addressed the main topics addressed in this investigation.

II. Methodology

With the aim of obtain the desired information to be analysed during the project a set of questions was prepared to be performed to players in the industry of cell therapies industry from different areas. 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.
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. 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.
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[6].

III. Cell Therapy Industry

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[2,7]. Despite the research related to the development of cell-based therapies have little over 50 years, cell therapy industry has shown a favourable market growth[8] 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].

The volatility associated with the cell therapy industry is derived by multiple causes. The emerging technologies have often some initial volatility followed by periods of stability and greater growth. At last, the causes unique to the cell therapy industry which are the disruptive nature of the technology 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[9]. 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 desired once the existent ones, used by the pharmaceutical industry does not fit correctly the nature and requirements of the cell therapy processes[10].

Although there are investments from the pharmaceutical industry in this area it is possible to verify some reluctance in investing[11]. 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[7,12].

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[13].

Although a recent business, cell therapy industries had already lucrative results. In 2010 the 20 cell therapies most sold produced revenues of about $460 million[8].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[11]. It is also expected an expansion of the market to $20 billion worldwide by 2025[14].

A. 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.

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 behaviour 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[15]

The Scientific Innovation model 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 emerged trying to place the product on the market at an earlier point in the innovation process. The Medical Innovation model is one of those new models composed only by 3 main phases: Basic Research, Product Development and Clinical Experimentation/clinical Application[16]. 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 analysed in our study.

B. 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[17].

1) Keys to successful commercialization

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[13]. 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[18].

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]

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[19]. 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.[20]

3) Business Models and Supply Chains

The unique characteristics and complexity associated to cell based products are leading to the emergence of new business models for regenerative medicine. 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[21]. 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 [24].

a) Autologous vs allogeneic products

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. 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 [22,23]. 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[24].

Autologous cell therapies are not “of the shelf products”, the need for cells collection from the patient implies proximity between the production site and patients or a system of collection of cells 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[22]. 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[25].

Allogeneic therapies allow the adoption of business and supply models comparable to the ones used by conventional biopharmaceutical companies, presenting commercial viability[26].These therapies are ready to apply, the manufacturing process is scalable and allow the possibility to compete against biologics and small molecules[25]. 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 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[28].

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[29].

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[30]. 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[31].

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[26]. 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.

C. 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[32].
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].In Europe, cell based therapies including substantially manipulated cells are included in the advanced therapy medicinal products (ATMPs) classification[33].

1) 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 [34]. 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".

2) Main criticism on hospital exemption

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.[35,36].
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[37].
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[38]. 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 disadvantage by the cell therapy companies[39] 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[38]. 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 [34].

IV. Data Analyses and Results

The use of mapping methods in this study was driven by the need of a qualitative data structuring method to apply in order to analyse complex information collected. 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.

A. Challenges in the cell therapy industry

According the responses it was identified that the main challenges could vary according the different geographic

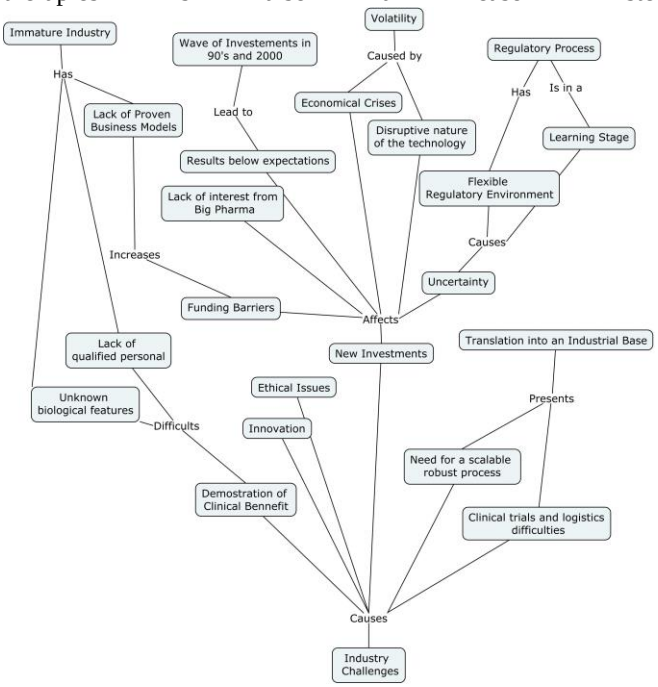
regions. The fact that the results of the first round of investments back in the early 90's and 2000 do not delivered the promise of the investments made, namely because although the recognized technological potential there were no unmet clinical needs addressed causing some pressure in the demonstration 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, 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 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 issue 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.

Figure 1 Schematic representation of influences related to the challenges faced by the cell therapy industry

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 behaviour 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 pointed. The lack of personal with formation and experience to deal with the unique features of the cell therapies is also a reason listed.



B. 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.

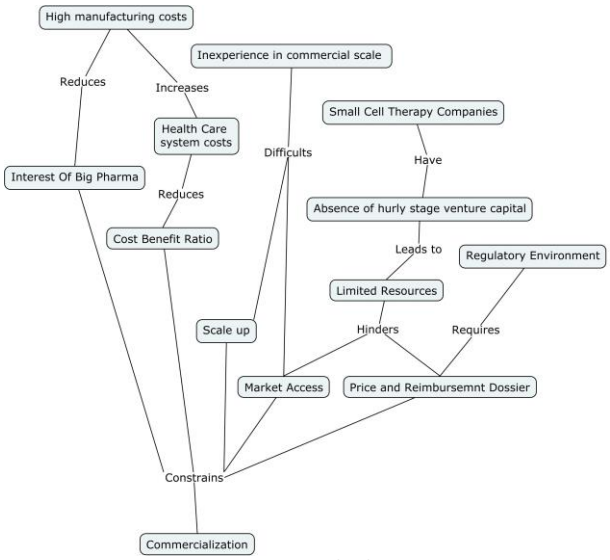


Figure 2 Schematic representation of influences related to the constrains to commercialization

C. 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 two of the research, 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.

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

The importance of the hospital exemption 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. This 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. The hospital exemption is considered a very useful tool that allows that in a European context the academic centres, together with local hospitals to be able to provide added value to individual patients with their researches.

The preservation of the hospital exemption is 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. 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 by 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 the 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 this 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.

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 should not be 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.

Figure 3 Schematic representation of influences of hospital exemption in the cell therapy markets

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.

E. 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 try 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.

Establishment of the value chains for the 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.

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.

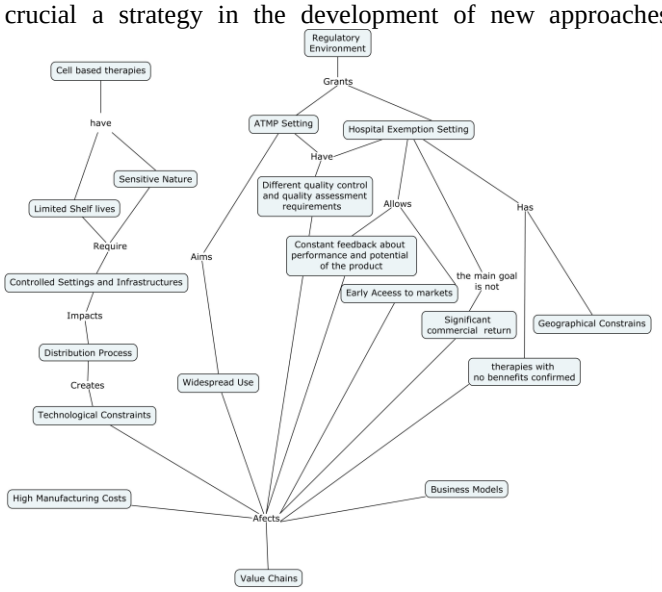


Figure 4 Major influences in the establishment of value chains in the cell therapy industry.

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.

1) Value chains: ATMP versus hospital exemption products

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 are 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 impacting 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.

F. 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 and the European Medicines Agency, have been made an effort to homogenize regulations regardless of geographic location and for scientific terms there is less and less differences. The efforts of both agencies to modernize and adapt to the needs and requirements of the complex nature of the cell therapy products are recognized. 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. 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 an opinion shared by members of the industry and academia that the regulatory agency responsible for acting in the US has 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. 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 or companionate use as parte as their regulatory strategy.

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.

G. Case study: 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 cm2 in size and has presented an acceptable safety profile according to the assessment implemented by the Committee for Advanced Therapies[40]. Currently already has been approved for reimbursement in Belgium, Netherlands and Spain.

The market where ChondroCelect competes is highly fragmented presenting several types of treatments for this pathology, namely, 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)[41]. 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.

1) 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.

V. 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 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 less subjected to risk. 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.

VI. References

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