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WHITE PAPER

CELL & GENE THERAPIES PROJECT

Focus on Logistical Challenges
"Patients can't wait and only have one chance"

FEBRUARY 2023

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1. Abstract

Pharma.Aero initiated the CGT Project to start exploring the fast-developing sector of the Cell and Gene Therapies (ATMP – Advanced Therapy Medicinal Products) and the particularities that have an impact on its logistics. The project's main goal was to broaden the current knowledge of this next generation market and offer a better understanding of its transportation requirements.

The CGT Project conducted by Pharma.Aero with the participation of its global network of pharma logistics stakeholders and several external partners and organizations offers a clearer view and a more detailed perspective on this emerging industry, identifies key logistical challenges and highlights some key points where the supply chain stakeholders could act.

2. Introduction

Pharma.Aero's mission is to achieve excellence in reliable end-to-end transportation of Life Science and MedTech products, by fostering collaboration between pharma-certified stakeholders dedicated to developing and pioneering the handling, storage and transportation of pharmaceuticals.

It is important for our organization to stay at the forefront of our industry's evolutions, therefore it is key to link up to the fast-growing sector of the CGT (or ATMP).

At the end of 2021, Pharma.Aero decided to launch the CGT Project, to explore the emerging ATMP (C&GT) sector, to raise awareness among the airfreight logistics providers on the specificities, challenges and opportunities presented by this rapidly evolving industry, and to lay the foundations of reliable supply chain logistics solutions.

3. Methodology

The project was designed in 4 Work Packages, each exploring the ATMP sector from a different perspective and with a specific approach:

- **Work Package 1:**
  Market Opportunity Analysis (March 2022)

  The project's first step was to run a market analysis by conducting a thorough desk research on value, type of products, products' requirements, current logistic capabilities and constraints. The results were published as a report destined for Pharma.Aero members and partners only.

- **Work Package 2:**
  Needs Assessment and Gap Analysis (June 2022)

  Following the Market Opportunity Analysis, the project team conducted a survey amongst the Pharma.Aero members and partners, to capture the level of knowledge, and interest in the ATMP sector and its logistical challenges and opportunities. 26 companies filled in the survey, including 3 pharmaceutical groups, 8 airports and 5 airlines. The survey explored multiple directions, from general knowledge on the sector and logistics, to certification aspects and interest in playing a more important role in the sector's logistics. The survey provided valuable information on directions worth being further explored and developed.

- **Work Package 3:**
  Pharma.Aero CGT Webinar (December 5th, 2022)

  Based on the results of the ATMP internal survey, Pharma.Aero organized a CGT Webinar to further deep-dive into the ATMP/CGT sector and its logistical requirements, Experts in the ATMP manufacturing and logistics sector shared first-hand insights and knowledge for a better understanding of the sector and its requirements.

- **Work Package 4:**
  Publications (January/February 2023)

  The project's findings and recommendations were published in a detailed Technical Report, available only to Pharma.Aero members and partners. This White Paper presents the project's methodology and the key takeaways to be shared with the industry.

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4. Results

4.1 Definitions and Framework

The ATMP (Advanced Therapy Medicinal Products) or CGT (Cell and Gene Therapies) are medicines for human use that are based on genes, tissues or cells.

The term ATMP (Advanced Therapy Medicinal Products) is used primarily in Europe to define medicines for human use that include gene therapy, somatic cell therapy, tissue engineering and advanced therapy combination medicines.

In the United States and elsewhere in the world, the term C&GT (Cell & Gene Therapies) is more commonly used.

We will zoom in more on the cell therapy part which is the most referred to when mentioning the ATMP sector.

Cell therapy is a therapy that treats a damaged organ or tissue in a patient's body using genetically modified cells that may come from the patient's own body (autologous cell therapy) or from a foreign patient (allogeneic cell therapy).

Physicians responsible for administering such treatments inject the therapeutic cells into the body of the sick patient after obtaining them from pluripotent or multipotent stem cells. Stem cells are cells that can self-renew, divide into different cell types, and reproduce. They are therefore of great interest in the field of cell and gene therapy because they can be used to treat or create a tissue or an organ due to their multiple functionalities.

Cell therapies are therefore unique, personalized treatments adapted and applicable to each patient. According to the EMA (European Medicines Agency), cell therapy is offering revolutionary opportunities for the treatment of severe and/or life-threatening diseases.

4.2 Market Potential

The global ATMP market was valued at USD 7.9 billion in 2020 and is expected to expand at a compound annual growth rate (CAGR) of 13.2% from 2021 to 2028 and to reach USD 21.2 billion by 2028 .

However, it is important to know that this market growth is the result of decades of progress and research that is only now paying back.

Today, there are hundreds of companies active in the ATMP clinical studies. In 2022, less than a dozen manufacturers received approval for new products.

Market activity in 2022:

2220
Active Clinical

202
Trials in Phase 3

+100
Gene Editing Trials

1457
Cell and Gene Therapy Developers Worldwide

The emergence of ATMPs has transformed the pharmaceutical industry and disease treatment landscape. This has led to new treatments and new ways of caring for patients.

Although this market segment is still new, we see this sector continuing to have a craze on the part of large pharmaceutical laboratories and Contract Manufacturing Organizations that continue to invest in these sectors, seeing them as important (and potentially profitable) solutions for therapies.

In 2023, not less than 14 market decisions are expected in the United States, while in Europe, a revision of the legislation is needed. The huge difficulties in reimbursement have complicated the patients' access to ATMPs: 7 of the 24 approved ATMPs have been pulled from the market.

The ATMP sector is most developed in North America with the largest share of revenues (47% in 2020). This is due to several factors, including strong innovation, a favorable regulatory environment and access to significant investment. Many clinical trials are conducted in the US, with 57% of gene therapy clinical trials taking place in the US by 2021.

Of the 1457 CGT developers worldwide, 47% are located in North America, 34% in the Asia Pacific region and 17% in Europe.

Asia Pacific
47% (492)

Europe
17% (244)

North America
47% (686)

Other Regions
2% (35)

4.3 Key Logistical Challenges

The ATMP sector, although a part of the biotech and pharma industry, is fundamentally different from the traditional pharmaceutical sector, and so are its logistical requirements.

It is extremely important to identify the aspects that differentiate it from the traditional pharmaceutical segment:

- **Starting material from patient**
- **Scarcity of resources / suppliers**
- **No inventories**
- **Timing / scheduling are critical**
- **Less equipment**
- **Each patient is unique**
- **Combining of different temperature ranges**

To fully understand the specific requirements of the sector, some key elements must be considered: **Criticality of the treatment, Life span of the product, Treatment costs.**

The challenges posed by the ATMP logistics can be classified as follows:

Product related
The products are unique and have very specific requirements

Process related
Processes related to the CGT industry are also generally more complex

Related to a Specific Stage of the Supply Chain
Specific issues arise in the different stages of the supply chain

Related to Competences and Know How
Specific knowledge is required

Technology related
Technological solutions represent a key element

Business related
This specific industry also generates specific actions and business approaches

Section 1: Product related

Most products require cryopreservation which is a complex process. Also, their transportation requires urgent action.

Temperature management

- The starting material is collected and shipped under ambient & controlled temperature to a – 80°C zone
- The apheresis from the patient is shipped to the manufacturing site at 2°C - 8°C temperature
- In case of remote production site, the material is shipped on dry ice.

Product stability

The stability of the product is controlled and monitored by various partners, whether at the level of broader services. It is also an obligation. However, the process does not always take into account all elements that can affect the product's stability (positioning in the box, shocks, etc.).

Good management of lead time

Lead time is a key element in this sector, as some products cannot be stored (autolog), and they have a brief life span between collecting the sample and administering the treatment. The patients themselves are in a critical condition and need the treatment as soon as possible. In the commercial production, there are often centralized units. Therefore, each country lead must also reserve production slots for patients, which can represent an additional challenge for the forecast and planning.

It is therefore of critical importance to limit the elements that can disrupt the lead time, particularly at airports.

Section 2: Process related

Whether by the nature of the products or the care to be provided to the patient, these treatments require urgent transport and rapid, qualified processes. Quality management is therefore a vital element.

Regular quality audits

Companies have created quality systems that integrate the logistical elements. For the larger players, SOPs are defined but do not always include all possible transport risks. The traceability and the monitoring of CAPA's at the partners' is however mastered.

Lane mapping

Companies need to do a thorough lane mapping for shipments, and take into consideration all elements that can have an impact on the security of the transport, such as customs specificities, holidays or complex periods, climatic risks, site-related issues, issues related to the technical aspects of an airport. This process could be improved.

Labelling

Labelling is generally under control as it is part of the GMP procedures. Traceability and safety requirements entail additional label specifications for ATMP packages and shipping containers.

In May 2022, EMA posted a draft guideline on labeling ATMP that contain genetically modified cells and requested feedback[4].

Risk Analysis

In general, it is noted that risk analyses underestimate a number of logistical and transportation aspects, despite the risks being thoroughly defined in the documentation.

It is important to develop a specific risk analysis for air transportation and to act by preventing the risks and building confidence. Some companies in Europe prefer road to air transportation, because of the bureaucratic complexity, but also because of the additional risks.

Standardization

Companies that are manufacturing commercial cell therapy products, follow specific protocols and procedures that are, also, mandatory for their partners, including hospitals. The protocols cover the logistics too. It is noted that, at this point, there is no harmonization, although the industry would benefit from defining and adopting a common set of standards. This could apply, as well, to other stakeholders, such as airports.

Section 3: Related to a Specific Stage of the Supply Chain

As Thomas Reid's stated, "a chain is no stronger than its weakest link", therefore it is important for us to evaluate all aspects of each entry or exit point in the supply chain. And airports are a key element. Here are some elements to take into consideration:

Capacity and availability of flights

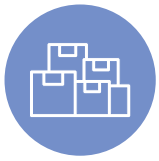
The COVID-19 pandemic presented us with a complex situation that resulted in a string of lessons learned. The capacity shortages observed during the COVID-19 period affect the sector's operability and the ongoing reorganizations may have an impact.

Airport capacity

The ability to handle ATMP quickly is key to an airport. It is, in some points, similar with transporting organs for transplant.

Knowledge of customs & Customs knowledge

Knowledge of customs procedures or specificities of customs offices, and zones, is relatively low. For start-ups and SMEs, it is mainly the laboratory staff who manages the shipments, and they lack knowledge in this area. There is therefore a heavy reliance on the logistics partner who also becomes a consulting partner and is integrated into the value chain.



On site storage

The various sites along the supply chain sometimes lack storage space and use dry shippers for temporary storage. Hospitals are sometimes forced to be innovative in storing products on a temporary basis.

Access to road networks, airports / network design

In the ATMP sector, there is a systemic lack of knowledge of the industry's networks, including hub & spoke organizations, transport networks, and other specific service providers. Generally, networks are defined more in terms of business objectives and not in terms of logistics specificities.

However, the choice of location for a production site is often linked to the presence of good airport and road infrastructures.

Natural disasters and environmental issues

In the context of cell therapy treatment, many imponderables can occur during the days or hours between the start and the end of treatment, including the impact of disasters and weather problems (storms or other extreme events). Given the criticality of some patients' conditions, stopping or delaying the treatment poses a major risk of death. Therefore, it is important to find alternative solutions quickly to deliver the products. Emergency solutions can be developed to complement standard solutions.

Real-time visibility

At the level of transport providers, there is sometimes a lack of real-time visibility of shipments. The technological progress provides us with new types of smart boxes or loggers. It would be a plus for companies if real time monitoring could also be achieved on the plane.

A number of starting materials are sourced from around the world and must therefore be transported internationally. It is important to be informed on the specific national legislation and be prepared, to avoid blockages and delays.

Handling capacity

Some airports may have little space of maneuver when it comes to the handling capacity, it is therefore important to take this element into account too.

Disruption & risks

Given the number of stages in the processing of a product at an airport and the various risks involved, ensuring fluidity around products is essential.

Section 4: Related to Competences and Know How

With such critical shipments, it is of paramount importance to train the staff and raise the level of knowledge on a certain number of logistics and transport issues: lane mapping, cold chain, incoterms, documents and administrative aspects, export procedures and trade, import & export strategies.

Section 5: Technology Related

Basic tracking of shipments & samples

Product traceability is relatively integrated, as it is part of the GMP requirements. This traceability is often used in passive mode and therefore rather reactive. There is a need for more integrated or technologically developed solutions such as packaging.

Implementation of technology (IT, ERP, TMS, WMS, orchestration platform)

The technological segment has a growing importance in the supply chain, but the level of digitalization of companies is still low for start-ups or still to be improved in some large companies. For smaller companies, there is sometimes a lack of ERP and good visibility on sample shipments or even the impossibility of connecting tools via API keys. This can be detrimental to the carrier.

The use of EDI is very low and they do not have a TMS. However, some companies have developed their own transport management and solution mapping tools. We are also seeing the emergence of orchestration platforms that increase the level of visibility.

Having a thorough and more accurate vision of the technologies' potential to contribute to the successful transportation of ATMP by air would be a plus for the industry.

Implementation of new technologies / Automation

Companies in the ATMP sector are constantly improving their production processes and this can significantly reduce treatment costs. Automation has thus become more important. From single batches, the industry should move into large scale production.

Automation will help unleash the full economic potential of ATMP in an ever-competitive drug market. Only then, with a positive cost-benefit ratio, living drugs will be appealing to healthcare providers and insurances companies. This will ultimately help to deliver more ATMP-based therapies to patients.

Transparency along the supply chain (e.g.: through blockchain)

Transparency and visibility are extremely important, and can be improved by better relations between partners, real time solutions, and the development of tools such as blockchain. Some companies are positioning themselves on this type of solution dedicated to the ATMP sector.

Section 6: Business Related

A certain number of challenges are specifically linked to the specific ATMP business models, while others are generally valid for the entire industry.

Externalizing vs Internalizing Logistics: the need to control

Some companies would prefer to internalize the logistics, to have better visibility and control of the samples. When externalizing logistics, the manufacturer does not have visibility over samples, especially for air transportation, at entry and exit points (impact of X-rays, handling re-icing, when necessary, custom controls, transit times, etc.)

Sustainability

Most companies are concerned about the overall environmental impact of their supply chain and therefore it is important to design and provide sustainable logistics solutions.

Scalability

Currently, only a few companies have the potential to scale up their production but others are emerging with growing potential for scaling up. For the moment, the number of treatments is fairly low, but in the coming years we might see it multiplied by 10 or 100. This will lead to a multiplication of logistical needs and challenges as well.

4.4 Project Outcome

The in-depth research conducted for the market analysis, the information gathered through the survey and the valuable insights offered in the CGT webinar, as part of the CGT Project, offered a wider and deeper perspective of the ATMP sector. Together with our members and partners participating in the project, the project team identified the challenges, but also the opportunities offered by the ATMP sector, particularly in relation to the airline industry. A number of key actions need to be taken to ensure the development of this industry.

Strengthen the skills of the players in the airfreight sector

The need to strengthen the skills of the airfreight stakeholders emerged from both the survey and the webinar. Participants expressed the need to keep up to date with developments in the sector, but also to increase internal skills. It is also important to be proactive and stay involved, as the rapid evolution of this sector results in continuously evolving needs.

Facilitate the flow of materials and substances

The great complexity of the CGT logistics sector stays in the diversity of its supply chain, involving multiple shipments for one treatment, various temperatures to be controlled, and the criticality of time. This project offers high level information on several key steps where risks arise. The airfreight sector needs to ensure a fluid flow. Also, that the legislative barriers need to be avoided. This also implies an increase in the knowledge of operators and customs officers.

Reduce time/ Eliminate time loss

The time loss can be eliminated through controlled processes, the use of adapted technologies, adequate training and adapted infrastructures. All these represent major elements for ensuring safe, and reliable ATMP logistics.

Identify products as specific to the CGT industry

It is important for the industry to design specific solutions for the CGT/ATMP logistics.

Limit regulatory constraints and upgrade CEIV

Over the years, the industry has been constantly improving its skills and knowledge of the pharmaceutical sector and its specificities. In this sense, the CEIV pharma certification has allowed many players to improve their level of expertise. However, this certification does not seem to be sufficient in view of the specific challenges of the ATMP sector. There is a need to reflect on the certifications and support to be implemented in the industry.

In general, the work on the regulatory elements likely to cause problems in the shipment of samples and products is an element of follow-up to be provided.

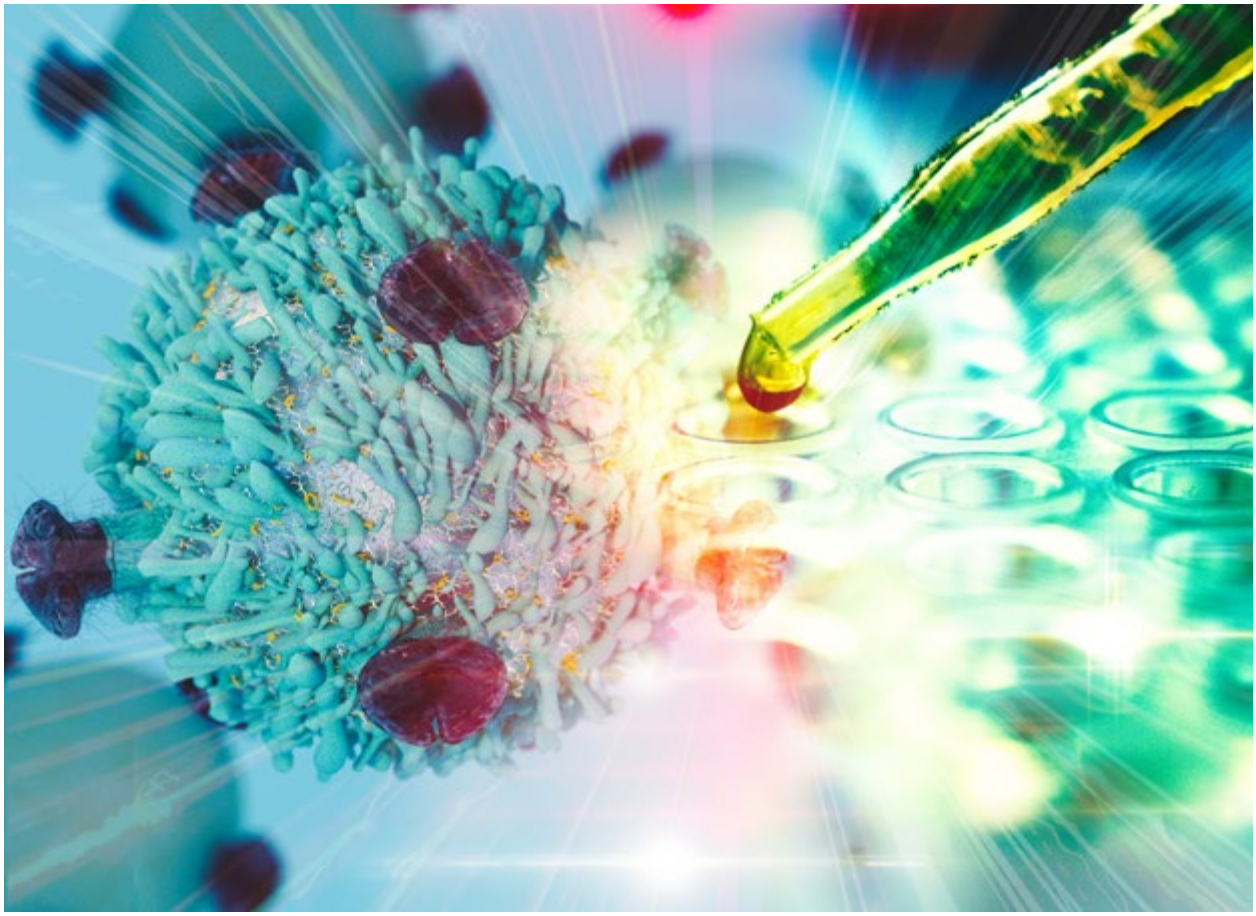
Pharma.Aero CGT Webinar – Insights

- *ATMP has a very complex and very intense supply chain – a high degree of coordination is needed at all stages of the supply chain.*
- *In some cases, for 1 European cell order, the EU Supply chain consists of 33 phases, including 6 courier shipments, 2 flights, 3 LN2 shippers and 1 Nanocool.*
- *Cell & gene supply requires 100% professionalism and does not allow any room for failure.*
- *There is a need for new ways of thinking, delivering and collaborating. Some initiatives are in place with organizations such as Pharma.Aero, OpenXcellerator, Bio Supply Management Alliance.*
- *New technologies are coming: 5G related devices, secure shipments using Artificial Intelligence, Risk mitigation tools and new types of packaging.*
- *Number of available CGT will increase significantly in the future*
- *Chain of identity and chain of custody are key. There is 1 unique batch, 1 patient*
- *There are different temperature ranges that should be combined. Vectors and plasmid, at – 65°C to – 70°C, while master cell banks and GMP cell banks need liquid nitrogen, and some products are handled at - 130°C*
- *Mapping of solutions are key: what choice of packaging type? What delays could occur?*
- *For some suppliers, there is only one company in the world, so you are very dependent.*
- *It is very important that the industry progress in terms of standardization, automation, HR & people, finances (products are not cheap, budget in industry going on - reimbursements will be key)*
- *There are different supply chains that are intertwined (Plasmid, Vector, DP), thus making the management even more complex.*
- *New supply chain management models are being implemented with control towers as in the examples given.*

5. Conclusion

As the ATMP (CGT) manufacturing sector is developing fast, so should the ATMP logistics branch, in order to keep up with, and even anticipate the continuously evolving needs and requirements of the ATMP. The CGT Project conducted by Pharma.Aero with the participation of its global network of pharma airfreight stakeholders represents only the start of exploring this sector. Our Market Opportunity Analysis, the CGT Survey and the CGT Webinar offered a clearer view and a more detailed perspective on this emerging industry, and highlighted some key points where the supply chain stakeholders could act. The current solutions in terms of certification, and training are not sufficient. It is therefore important to continue the work with the implementation of specific actions.

As an additional positive result of Pharma.Aero's CGT Project, many links have been established with industry organizations, manufacturing companies and other, highly specialized, supply chain stakeholders. Pharma.Aero will capitalize on these connections and brainstorm on projects ideas and other types of collaboration to continue to raise awareness and increase the level of knowledge in the ATMP logistics industry.



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Acknowledgement

Within the framework of this project, various collaborations have been set up, with the participation of several external partners and organizations, thus allowing us to broaden our vision of the sector and the stakes.

We would like to sincerely thank Rebecca Karp from Taysha Gene Therapies and Geoffrey Sargent from GeneTether Therapeutics.

Many thanks to all our webinar speakers for sharing valuable insights and expertise: Andreas Olpeter, Andy Faes, Cristian Circiumaru, Diego Loaiza, Erik Agterhuis, Guy De Meester, Kathleen M. Otto, Michael De Beuckelaer, Victor Adeniyi.

Thank you to all Pharma.Aero members for completing the survey. Special thanks to our Pharma.Aero project team and partners

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