WHITE PAPER
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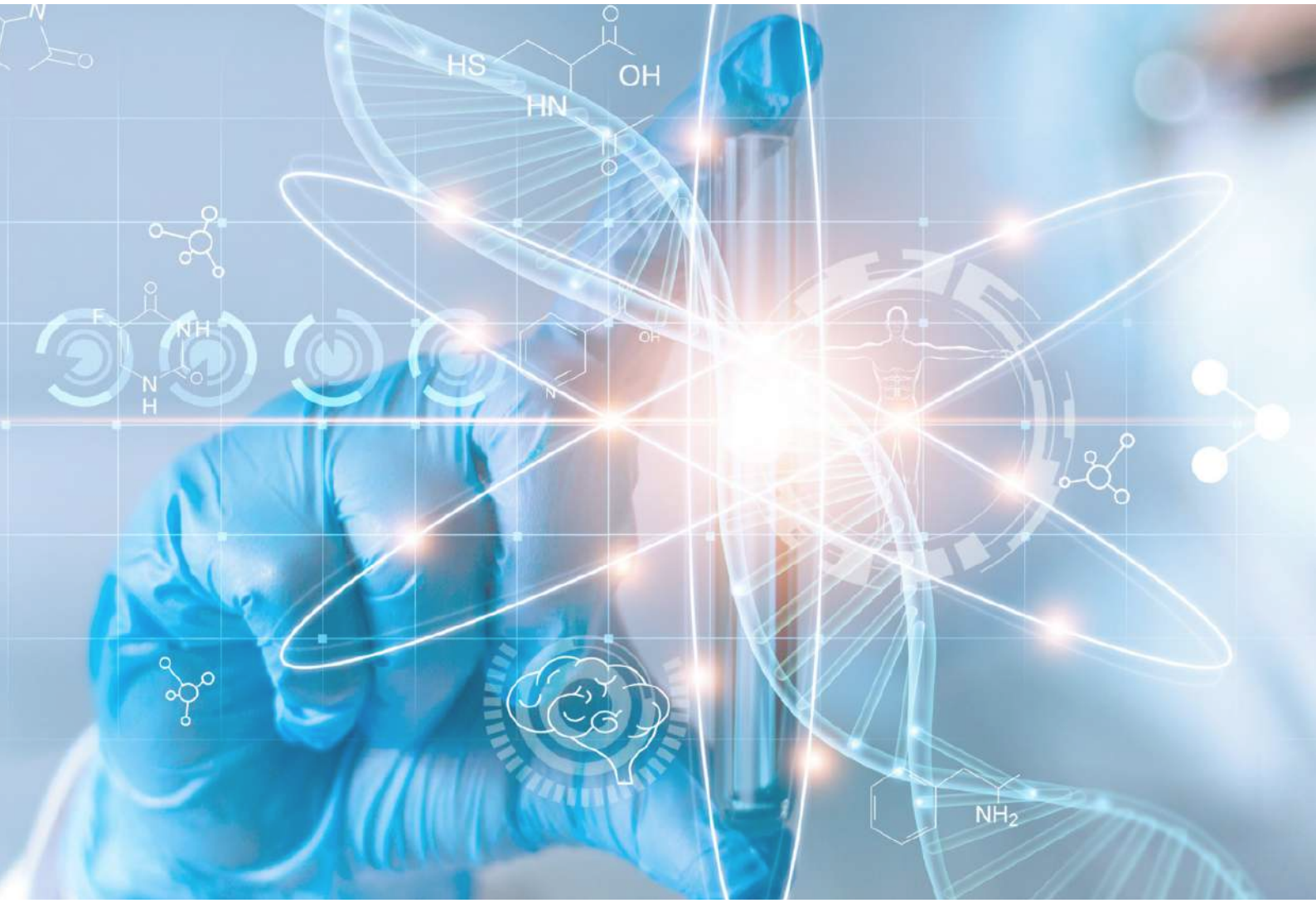
PRECISION THERAPY LOGISTICS PROJECT



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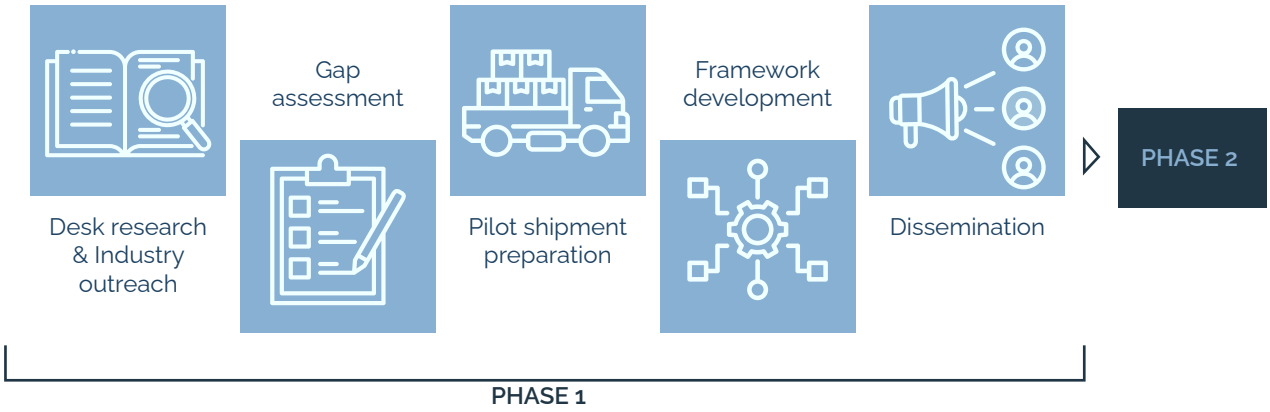
ABSTRACT

Precision therapies represent a significant advancement in the field of healthcare. By leveraging health data from individual patients to personalize treatments to their specific condition, they enhance the efficacy of treatments, reduce adverse side effects, and improve overall patient outcomes.

As a result, the market for precision therapies is growing significantly, with thousands of clinical trials ongoing globally and numerous therapies already approved by the authorized regulators. However, delivering these therapies to patients safely and timely poses significant challenges due to their product specifications.

Recognizing the critical importance of precision therapies and their logistics, Pharma.Aero initiated the Precision Therapy Logistics (PTL) Project to explore the specific requirements for their handling and distribution. The project successfully established a logistics framework for the safe, secure, and effective distribution of precision therapies, identifying eight interconnected areas of focus. This achievement paves the way for the larger PTL Gateway Project, which will build on this foundation to develop standard operating procedures (SOPs), standardized international shipping criteria, including an official label, and other initiatives to ensure proper product handling and distribution.

METHODOLOGY



To limit the scope of this project, only ATMPs (Advanced Therapy Medicinal Products) and RLTs (Radioligand Therapies) were analyzed. The project explored the different types of ATMPs and RLTs as classified by regulatory standards. Thereafter, the logistics considerations of these therapies were researched, with which the different classes could be grouped together based on their identified similarities.

Based on the identified logistics considerations, a gap assessment was performed to decide which therapy classes to include within the scope of the pilot shipments. However, during the preparation of the pilot shipments, critical considerations emerged that prompted the reassessment of the project's initial scope. Consequently, no pilot shipments were conducted during the first phase of the project, with no major impact on the overall outcome.

The logistics framework was developed based on findings from the research, survey, interviews and workshops to highlight focus areas necessary for the safe, secure and effective distribution of precision therapies. These focus areas range from end-to-end real-time shipment visibility to standardized product labeling and will provide the starting point for subsequent project phases.

Project team composition

NAME	ORGANISATION	PROJECT ROLE
Samuel Speltdoorn	Brussels Airport	BOD Liaison
Roland Yap	Novartis	Project Lead
Milton De La Paz	Dallas Fort Worth Airport	Project Lead
Frank Van Gelder	Pharma.Aero	Secretary General/ Editorial Review
Sara Van Lerberghe		Project Coordinator/ Editorial Review
Alice Iacobescu		Editorial review
Nassim Benhamou	PwC	Project Manager
An D'hondt		Project Experts
Natalia Violato		
Morgane Franck		

INTRODUCTION

1. PROJECT OBJECTIVES

The Precision Therapy Logistics project was initiated by Pharma.Aero to raise awareness and investigate the specific challenges, to be able to create specific standards and guidelines that can serve as an international model for the secure and effective distribution of patient-critical, fragile and valuable medicines.

2. THERAPY FRAMEWORK

Precision medicine tailors treatments to the individual patient in order to improve their effectiveness, whereas traditional medication often follows a one-size-fits-all approach, where treatments are designed more for the average patient without considering individual differences. As a result, precision medicine is also referred to as personalized medicine.

Personalized medicine's benefits

Improved therapy efficacy and reduced negative side effects

Better prediction and prevention of diseases

Reduced hospitalization

More effective and efficient clinical trials

Overall better quality of life for patients

Advanced therapy medicinal products

ATMPs are medicines for human use based on genes, cells or tissues. The term ATMP is mostly used in Europe, whereas in the US the terms "cell and gene therapies" or "regenerative medicine" are more common.

The global market for ATMPs, valued at USD 14.6 billion in 2024, is projected to quickly grow to USD 35.6 billion by 2032, with a CAGR of 11.8%[1]. This expansion can be largely attributed to the fact that ATMPs often address rare and severe diseases with significant unmet medical needs by targeting the root cause of the disorder. Consequently, these therapies offer long-lasting relief with just one or a few administrations.

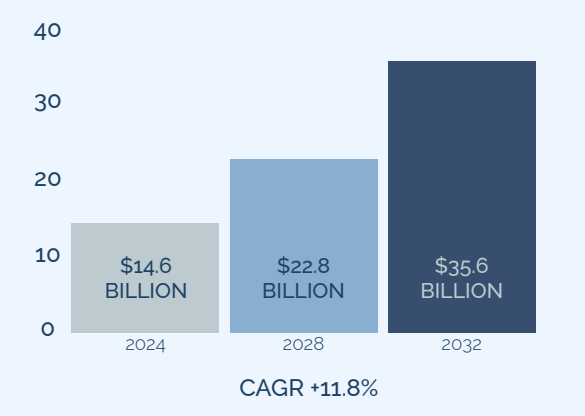


Figure 1

27 ATMPs have already been approved by the European Medicines Agency (EMA)[2] and 38 by the Food and Drug Administration (FDA)[3], with over 60 global launches expected between 2024 and 2030[4]. The hundreds of ongoing clinical trials globally strengthen this positive trend (figure 2)

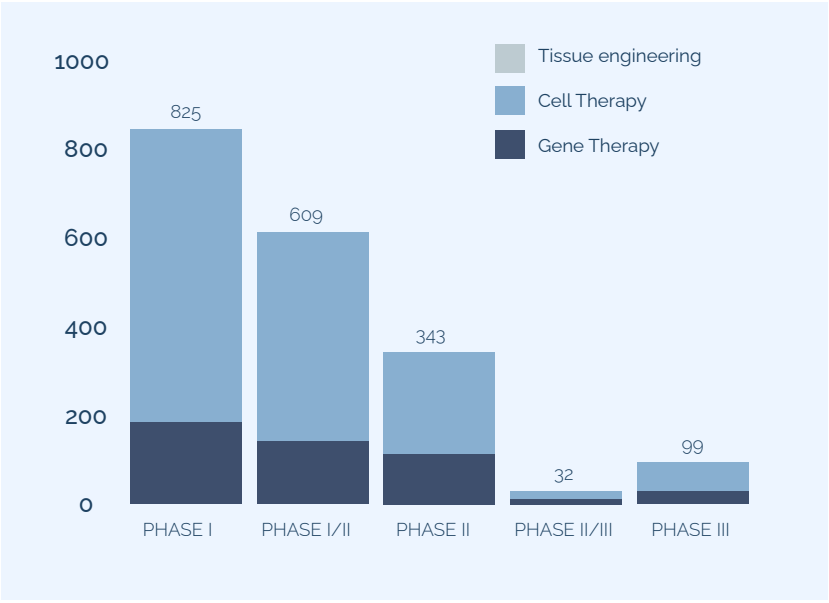


Figure 2: Global clinical ATMP trials by therapy type (ARM, 2024)

1 Straits Research (2024) Advanced Therapy Medicinal Products (ATMP) Market Size by 2032

2 European Medicines Agency (2024) CAT quarterly highlights and approved ATMPs

3 Food and Drug Administration (2024) Approved Cellular and Gene Therapy Products

4 Italian National Institute of Health (2024) Terapie avanzate: entro il 2030 fino a 60 nuovi farmaci, ma per assicurare equità e sostenibilità servono nuovi modelli di accesso

ATMPs treat various conditions ranging from sickle cell disease to spinal muscular atrophy. However, 3 in 4 ATMPs are oncology-focused (figure 3).

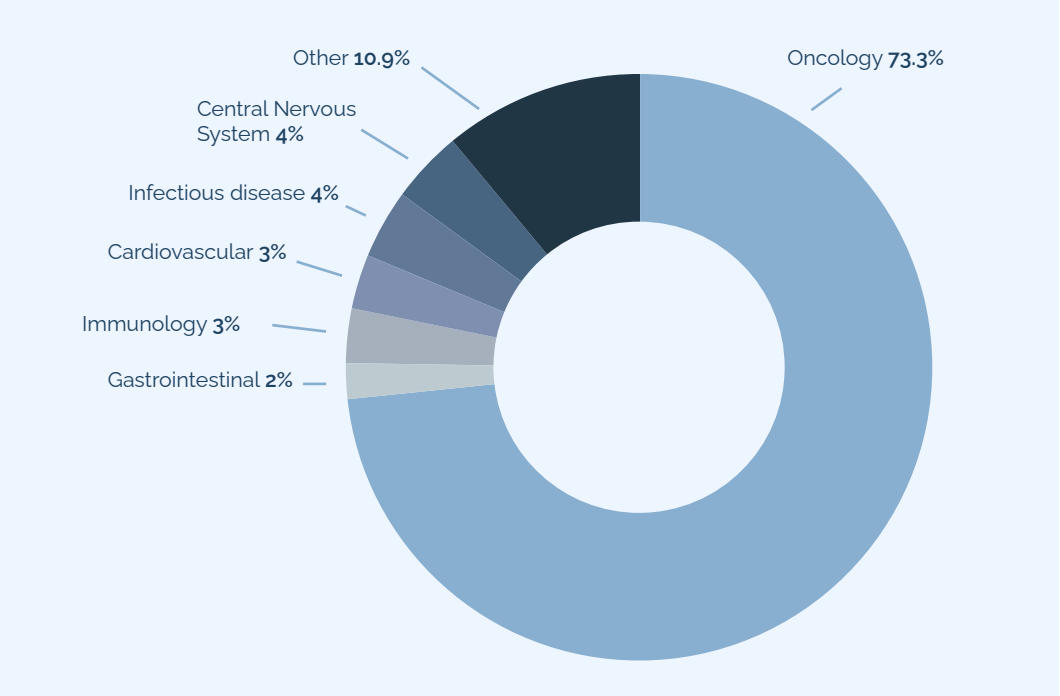


Figure 3: ATMP clinical focus (ARM, 2024)

The European Medicines Agency divides ATMPs in four classes:

GENE THERAPY MEDICINAL PRODUCTS (GTMP)
recombinant genes, created in a laboratory to treat genetic disorders

CELL THERAPY MEDICINAL PRODUCTS (CTMP)
manipulated cells or tissues to perform a specific function in the body

TISSUE ENGINEERED PRODUCTS (TEP)
modified cells or tissues to repair, regenerate or replace human tissue

COMBINED ATMPs (cATMP)
combinations of an ATMP with a medical device

a. Gene Therapy Medicinal Products (GTMP)

GTMPs leverage genes to prevent or treat diseases. This grants them the ability to eradicate the root cause of a condition by addressing the underlying malfunction (e.g., a mutated gene).
Gene therapies have different treatment modality, as the product can be administered "in vivo" or "ex vivo".
In vivo gene therapies involve directly inserting functional copies of a gene into target cells within the body to correct or replace faulty or missing genes.
Ex vivo gene therapies consist of removing specific cells from a person, genetically altering them in a laboratory, and then transplanting them back into the person.

b. Cell Therapy Medicinal Products (CTMP)

In essence, CTMPs are treatments that harness living cells to combat diseases. These cells can be modified or used to perform different functions compared to their original state and are designed to leverage their biochemical activities to provide therapeutic relief. These therapies are also referred to as somatic cell therapy medicinal products.
These therapies can be either autologous or allogeneic.
Autologous therapies use a patient's own cells. These cells are collected, modified or expanded in a laboratory, and then reintroduced into the same patient.
Allogeneic cell therapies use healthy cells from a donor. These donor cells are processed and administered to a patient who may not have enough healthy cells of their own. Despite being cell-based, EMA classifies CAR T-cell therapies as ex vivo GTMPs as opposed to CTMPs.

c. Tissue Engineered Products (TEP)

TEPs are classified by EMA as products that:
• Contain or consist of engineered cells or tissues, and
• Are presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

Similar to CTMPs, tissue therapies can be autologous or allogeneic, depending on whether the material is sourced from the patient or from a donor.

d. Combined ATMP (cATMP)

EMA defines cATMPs as ATMPs that fulfill the following conditions:
• They must incorporate, as an integral part of the product, one or more medical devices, and
• Their cellular or tissue part must contain viable cells or tissues, or
• Their cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

Fundamentally, cATMPs are medical devices integrated with a GTMP, CTMP or TEP.

ATMP class and modality overview

GTMP	In vivo	Functional genes are directly inserted into the patient	Luxturna USD 0.85 mln[5]
	Ex vivo	Patient cells are modified outside of their body	Casgevy USD 2.20 mln[6]
CTMP	Autologous	Therapy consists of patient cells or tissues	None approved yet by EMA
	Allogeneic	Therapy consists of donor cells or tissues	Omisirge USD 0.36 mln[7]
TEP	Autologous	Therapy consists of patient cells or tissues	Holoclar USD 0.10 mln[8]
	Allogeneic	Therapy consists of donor cells or tissues	Rethymic USD 2.82 mln[9]
cATMP		Medical devices combined with a GTMP, CTMP or TEP	None approved yet by EMA

5 Drugs.com (2024) How much does Luxturna cost?.
6 Reuters (2023) Vertex/CRISPR price sickle cell disease gene therapy at $2.2 mln
7 Drugs.com (2024) Omisirge Prices, Coupons, Copay Cards & Patient Assistance
8 National Institute for Health and Care Excellence (2017) Final appraisal determination
9 Maragkou, I. (2024) The most expensive drugs in the US

Radioligand Therapies

RLTs are a relatively new approach to treat cancer. These therapies employ radioligands to deliver targeted radiation directly to specific types of cells, significantly enhancing the overall survival and quality of life for cancer patients. Radioligands are composed of two key components: a ligand and a radioisotope. Although this novel approach is more expensive than traditional cancer treatments, its effectiveness and safety make it a promising future option in oncology. This is supported by many ongoing clinical trials and approved treatments.

Cancer cell receptormolecule connecting with radioisotope & ligand

Radioisotope

Ligand

RESULTS

1. LOGISTICS CONSIDERATIONS

Product Journeys

In order to analyze ATMPs and RLTs from a logistics perspective, they were first clustered by accounting for product and supply chain factors such as temperature sensitivity, production strategy and product uniqueness. This allowed four product journeys to be discerned:

In vivo GTMP	Autologous therapy (including ex vivo GTMP, CTMP and TEP)
Allogeneic therapy (including ex vivo GTMP, CTMP and TEP)	RLT

These journeys have thereafter been further outlined and examined in order to determine their logistics similarities and differences. Due to their rarity and a lack of available information, cATMPs were omitted from the product journeys.

In vivo GTMP	Autologous		Allogeneic	RLT
No patient or donor material required for production	Patient material is collected, processed, and re-administered	STARTING MATERIAL 	Donor material is collected, processed, and administered to the patient	No patient or donor material required for production
Manufactured for multiple patients	Manufactured for individual patient	UNIQUENESS 	Manufactured for multiple patients	Manufactured for multiple patients
Package-to-Order	Make-to-Order (vein to vein)	PRODUCTION STRATEGY 	Make-to-Order or Package-to-Order	Make-to-Order
-60 to -80°C	Cells: -120 to -196°C Tissues: 15 to 25°C, 2 to 8°C	TEMPERATURE REQUIREMENTS 	Cells: -120 to -196°C Tissues: 15 to 25°C, 2 to 8°C	Highly product-dependent: from 15 to 25°C down to -60 to -80°C
No	No	RADIOACTIVE 	No	Yes
Passive dry ice shipper[10]	Cells: passive cryogenic shipper[11] Tissues: passive shipper	PACKAGING 	Cells: passive cryogenic shipper Tissues: passive shipper	Lead containers and Type-A packaging for radiation shielding
Months to years (frozen)	Cells: months to years (cryo-preserved) Tissues: hours to days (fresh)	SHELF LIFE 	Cells: months to years (cryo-preserved) Tissues: hours to days (fresh)	Days
Up to millions of USD	Generally, less expensive than in vivo GTMPs (below USD 1 mln.)	PRODUCT VALUE 	Generally, less expensive than in vivo GTMPs (below USD 1 mln.)	Up to hundreds of thousands of USD (full treatment)
Lower than autologous due to buffer stock of finished product	Extremely high as patient material required for production	LOGISTICAL FAILURE IMPACT 	Extremely high in Make-to-Order, but lower in Package-to-Order	High due to short shelf life and demand-based production
Easier to scale due to regional inventory opportunities	Difficult due to vein-to-vein supply chain setup and product uniqueness	SCALABILITY 	Difficult for Make-to-Order, but easier for Package-to-Order	Decentralized production necessary to scale due to low required lead times
Specialized white-glove shipping services	Specialized white-glove shipping services	PARTNER COMPETENCIES 	Specialized white-glove shipping services	Nuclear medicine handling & transportation & white-glove shipping services.

10 Passive shipper using solid carbon dioxide (dry ice) to keep products frozen, applicable from -20 to -80°C

11 Passive shipper able to maintain temperatures below -120°C, for example through the use of liquid nitrogen as a coolant

In-Vivo Gene Therapies

Since in vivo GTMPs do not rely on patient material, the supply chain follows a Package-to-Order strategy to increase responsiveness to patient demand. This strategy means that the product is produced and stored based on forecasts, whereas final packaging, labeling and distribution are executed only when an actual order is received.

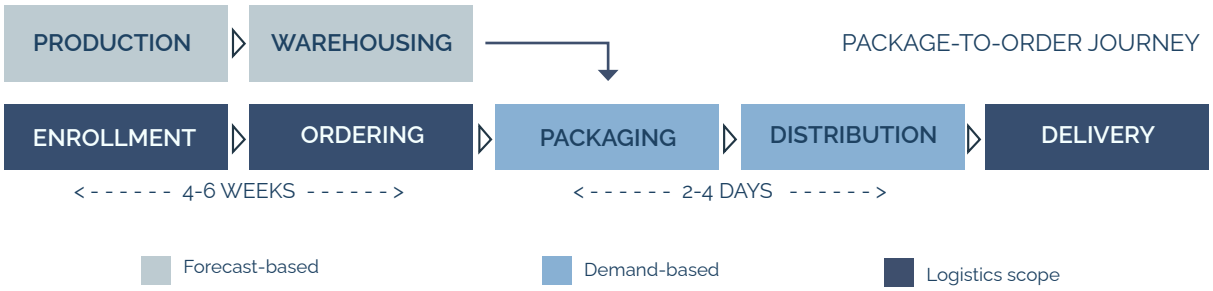


Figure 4 : In vivo GTMP journey - Package-to-Order

Consequently, to preserve product stability, the GTMP is deep frozen at temperatures ranging from -60°C to -80°C following production, and stored at a (regional) packaging site. Once a patient enrolls at a hospital, their eligibility is checked and a delivery date set, an order can be created and verified against available inventory. The treatment dose is moreover tailored to the specific characteristics of the patient.

Once verified, the order is released to the relevant packaging site, after which the vials are selected, thawed, labeled, and re-frozen. These vials are then packaged in dry ice shippers to maintain the required freezing temperatures during transportation. The product typically needs to reach the patient within a few days of pick-up due to its criticality and fragility.

Thus, white-glove shipping services are contracted. These services involve specialized handling and expedited transportation to ensure the safe and quick delivery of critical and fragile products. Proper hospital storage methods are also implemented to guarantee correct product receipt, whereafter the therapy can be administered to the patient, completing its product journey.
Although it can take several weeks before a therapy is administered once a patient enrolls, the logistics scope (final packaging and distribution) must be fulfilled in a couple of days.

Autologous Therapies

Autologous therapies follow a closed-loop or “vein-to-vein” process, where the supply chain starts and ends with the patient.

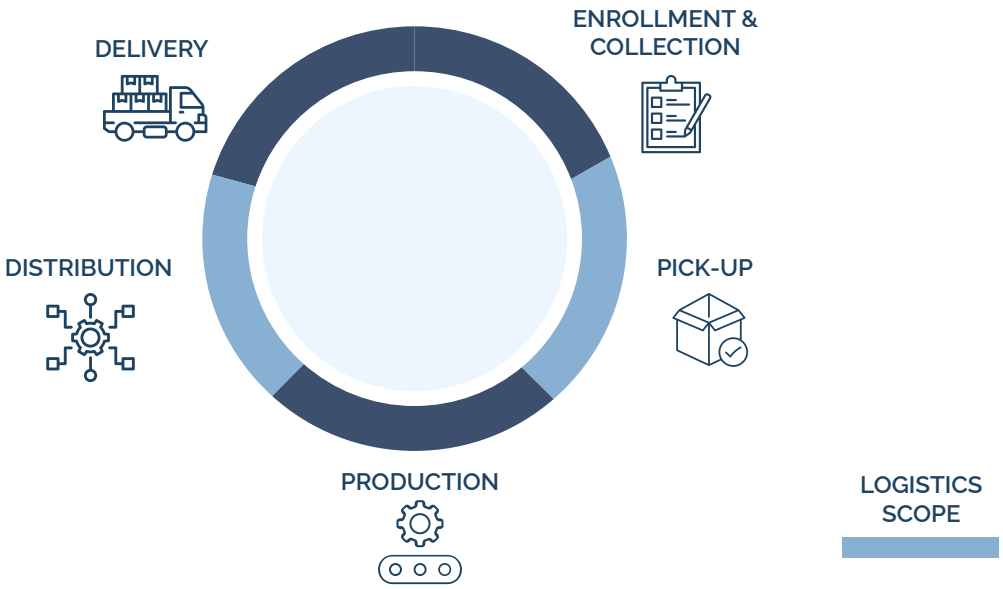


Figure 5 : Autologous therapy journey

The journey begins with the patient enrolling at the treatment center, triggering the supply chain. The material (cells or tissue) is collected from the patient through procedures such as apheresis. Once obtained, the material is uniquely associated with the patient to maintain the chain of identity from this point forward.

Following collection, the material is picked up and transported to the manufacturing facility, often under strict cryogenic conditions (temperatures below -120°C). The chain of custody ensures that the material’s location is continuously tracked through the supply chain, preserving its integrity and identity. At the manufacturing facility, the material is thawed, modified to the patient’s specific condition, and then repackaged for return. This production process is known as Make-to-Order, where the product is customized to the needs of the patient.

The final stages of the journey involve the distribution and delivery of the engineered material back to the treatment center, using specialized white-glove shipping services due to the high risk and value involved. Upon arrival, careful coordination between stakeholders ensures an efficient handoff, before the therapy is administered to the patient. Because patient material is used, any disruption in this process can result in significant delays and potentially having to restart the entire process, which can last three to five weeks.

Allogeneic Therapies

As previously mentioned, allogeneic therapies are more "off-the-shelf" since they are based on donor material rather than the patient's own. The absence of a closed-loop system allows these therapies to be produced at a larger scale, making their supply chains more responsive compared to autologous therapies.

Figure 6: Allogeneic therapy journey – Make-to-Order

As such, donor material can either be collected on-demand after patient enrollment or be pre-collected and stored (for example, in a biobank). The material is modified to the patient's condition at a production facility, before being labeled, packaged and shipped to the treatment center. The responsiveness of the supply chain is lower in this case, although logistics lead times remain short. The risk is furthermore higher in case of a deviation as there is no inventory to fulfill demand from. An example of such a therapy is Rethymic, an allogeneic TEP developed by Enzyvant, which uses donor thymus tissue to treat congenital athymia in children.

Shipping Non-Frozen

While many autologous and allogeneic therapies require cryogenic temperatures, the optimal temperature can vary significantly from product to product. Some TEPs, for example, are shipped fresh rather than frozen due to the challenges of safe freezing. Holoclar is a notable example, with a recommended storage temperature of 15 to 25°C[12]. Handling these products at higher temperatures presents several trade-offs that can be assessed across the same four key dimensions: product, process, technology, and people and partners.

12 Joyce, K., Buljovcic, Z., Rosic, G., Kaszkin-Bettag, M., & Pandit, A. (2023). Issues with Tissues: Trends in Tissue-Engineered Products in Clinical Trials in the European Union. Tissue Engineering Part B: Reviews, 29(1), 78-88.

Radioligand Therapies

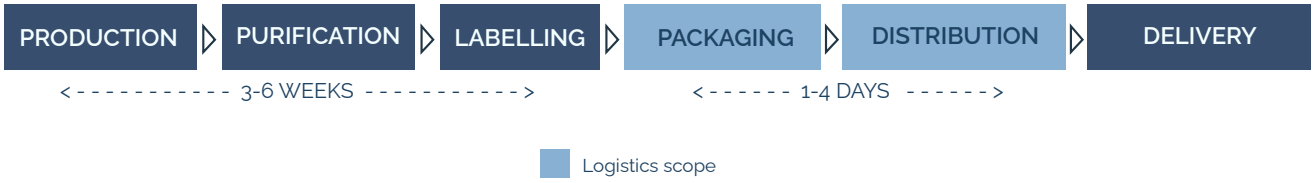


Figure 7: Radioligand Therapies journey

RLTs rely on a streamlined and secure supply chain due to their radioactivity and extremely short shelf life. The production process is driven by actual demand, considering the rapid decay of the isotopes involved. Ideally, the production is decentralized, leveraging local facilities to meet stringent lead time requirements. The journey of RLTs begins with the enrichment of minerals in nuclear reactors to create radioactive isotopes, which are then purified and concentrated into a liquid salt solution. This solution is quickly labeled and attached to targeting molecules (ligands) to form the final RLT product. Once production is complete, RLTs are packaged according to international safety standards in small lead containers that block radiation.

These containers are then placed in Type-A packaging to ensure proper handling, shielding, and temperature control during transit. The isotopes' radioactive decay underlines the need for efficiency throughout the supply chain. After quality inspections, the packaged RLTs, with a remaining shelf life of 2-5 days depending on the isotope, are shipped to the hospital as quickly as possible.
The complexity of transportation is heightened by the regulatory constraints on radioactive materials and the need for reliable logistics partners capable of rapid and secure delivery. At the hospital, the treatments are administered promptly, often requiring patients to be isolated in lead-lined rooms. The disposal of radioactive waste is carefully planned, adhering to processes specific to each isotope to ensure safety and compliance with health regulations.

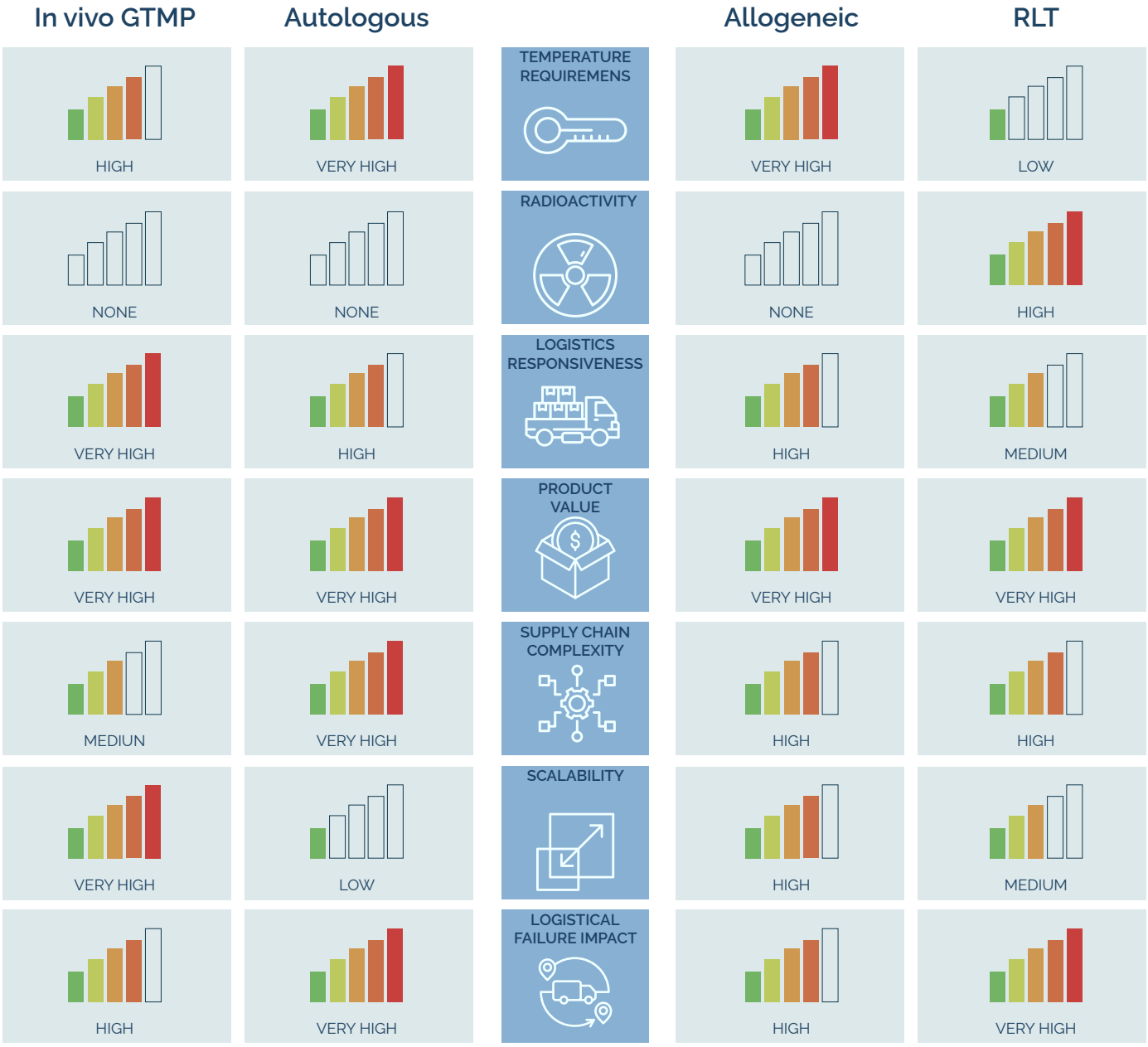


Figure 8: Qualitative product journey comparison

The comparison shown in figure 8 is a high-level qualitative assessment as different products with a similar journey might possess varying characteristics. Moreover, this comparison is relative only to the listed product journeys.

Logistics Considerations Overview

Seeing as how the logistics scope covers many aspects related to the product and its distribution, the different considerations are grouped into four categories in order to structure the analysis. Some of the considerations apply to multiple product journeys, while others are more specific.

The table below briefly lists the defining considerations for the four product journeys identified in the previous section. These considerations are again divided into the same four categories.

	In vivo GTMP	Autologous	Allogeneic	RLT
PRODUCT 	• Deep frozen • Extremely high value • Not patient unique	• Varying temperature ranges • High value • Patient-based	• Varying temperature ranges • High value • Donor-based	• Radioactive • High value • Extremely short shelf life
PROCESS 	• Package to Order • Forecast-based production • Use of inventory • Higher scalability	• Make to Order • High complexity due to vein-to-vein supply chain • Lower scalability	• Make or Package to Order • Lower complexity due to the use of donor material • Higher scalability	• Make to Order • Stringent safety standards • Scalability requires
TECHNOLOGY 	• Real-time monitoring • Stakeholder alignment • Order translation into correct pick and pack activities	• Real-time monitoring • Critical chain of identity • Close integration with treatment centers	• Real-time monitoring • Stakeholder alignment • Efficient donor material sourcing and matching	• Real-time monitoring • Clear product labeling • Efficient
PEOPLE & PARTNERS 	• End-to-end training for safe product handling • Clear escalation procedures • Focus on quality instead of cost for partner selection	• Additional attention to safety in case of cryopreservation • Clear escalation procedures • Importance of smooth handoff	• Additional attention to safety in case of cryopreservation • Clear escalation procedures • Importance of smooth handoffs	• Additional attention to security due to radioactivity • Enforcing regulatory standards • Alignment on risks and responsibilities

2. LOGISTICS FRAMEWORK

Framework Overview

The logistics framework was developed by consolidating findings from the research and industry outreach, highlighting focus areas critical for the distribution of precision therapies, ATMPs and RLTs in particular. These focus areas address common industry challenges such as end-to-end coordination and quality control. This framework not only identifies avenues to further pursue in the second phase of the PTL Gateway project, but it also enables therapy developers and their partners to align on the necessary elements for safe and responsive product delivery.

As figure 9 illustrates, the framework consists of eight focus areas ranging from dedicated project teams to logistics visibility.

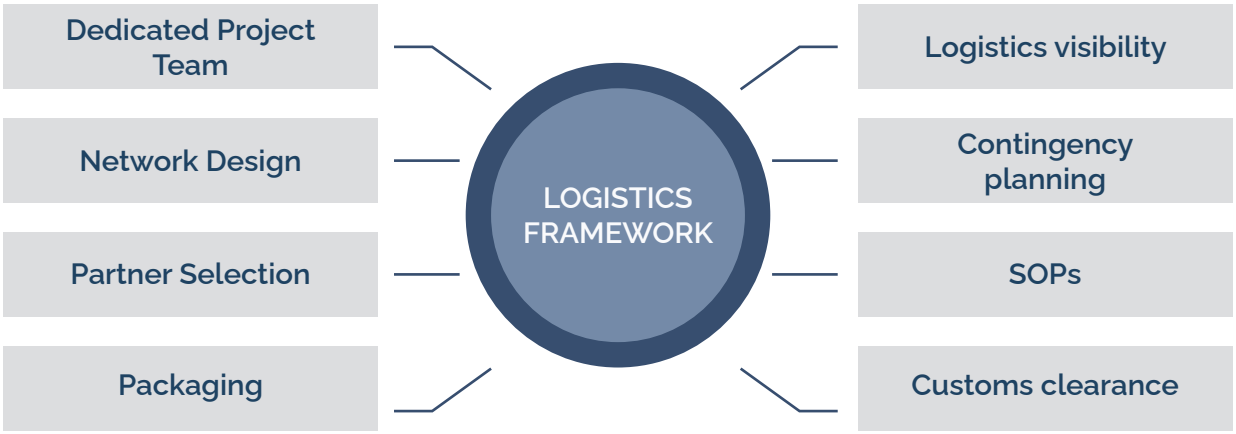


Figure 9: Logistics framework

While these focus areas may seem distinct at first, many interdependencies exist between them. For example, the level of logistics visibility depends on the applied traceability system, often provided by partners such as freight forwarders or solution providers. Similarly, standardized product labels can streamline customs and airport processes. Essential elements such as operator training and temperature control are integrated across multiple focus areas, reflecting the need for a holistic approach that encompasses people, process and technology perspective in precision therapy logistics.

PROJECT TEAM 	• Dedicated project teams have expertise in handling and transporting sensitive precision therapies • With cross-functional responsibilities, they provide quick and effective support if issues arise during the distribution process • They ensure seamless stakeholder coordination and adherence to logistics requirements • These teams are important because precision therapies require customized processes, hold significant risk, and need comprehensive coordination
NETWORK DESIGN 	• The design of the distribution network should facilitate responsive and efficient product delivery in a scalable manner • This typically involves streamlining logistics in terms of transportation mode, partners and nodes to minimize risk and reduce order fulfillment time while maintaining product quality • To increase responsiveness, opportunities are being explored to decentralize distribution networks and bring them closer to the patient (e.g.: Package-to-Order strategies, GMP-in-a-box technologies etc.) • Although less complex, these decentralized processes necessitate more oversight to guarantee compliance
PARTNER SELECTION 	• There must be a common understanding across logistics partners (e.g.: freight forwarders, airlines, and packaging providers) on the importance and urgency of these shipments • This translates into specific capabilities regarding packaging, temperature control, quality standards (e.g.: GDP or CEIV certification), system integration, geographic network, service level, etc. • In addition to possessing adequate expertise, a clear allocation of responsibilities and open communication channels are essential to accurately and efficiently convey shipment requirements (e.g.: the arrival time for pre-conditioned packaging) • Incorporating backup partners and services into the network is critical to ensure continuity during disruptions
PACKAGING 	• Specific product requirements necessitate the use of specialized packaging to maintain optimal conditions or provide protection, • These therapies often qualify as dangerous goods due to the product (e.g.: radioactive) or its packaging material (e.g.: dry ice), which involves additional regulatory guidelines and specific stakeholder training • Product labeling maintains the chain of identity, but can also inform to stakeholders of the product type, handling needs and urgency • A standardized shipping label can facilitate product handling in airports, for example by making the therapies visually identifiable

LOGISTICS VISIBILITY 	• Considering the criticality and sensitivity of the shipment, an end-to-end and real-time view on the shipment's location and condition enables precise coordination and quality control • This visibility needs to be end to end as logistics requires close integration across multiple stakeholders and any failure may gravely affect the product or its delivery • Through real-time tracking, interventions can occur proactively to prevent issues from materializing or aggravating Continuous temperature monitoring allows for the calculation of • a stability budget to prevent every temperature excursion from demanding immediate involvement • Key properties of such an overarching visibility system are: transparency, integrity, granularity, interoperability, security and compliance
CONTINGENCY PLANNING 	• Logistics visibility yields value only when the insights gained are actionable, necessitating the development of a contingency plan • This plan highlights risks along the logistics process, assesses their potential impact and identifies adequate control measures • Multiple methods exist to develop such a plan: what-if analysis, failure mode and effects analysis, fault tree analysis, etc. • Effective communication and training are essential to align stakeholders on the correct actions to perform in the event of a disruption
SOPs 	» Validated procedures guide the end-to-end logistics process by establishing effective coordination, communication and quality control » Thorough training on these SOPs is critical due to the specificity of precision therapy logistics and its associated risks » These protocols should not only describe shipment preparation, but also refer to the contingency plan, communication matrix and allocation of responsibilities
CUSTOMS CLEARANCE 	• As customs may cause significant, unforeseen delays, close collaboration with customs authorities and regulatory compliance are essential • Next to preparing the correct documentation, proactive communication with customs is key to better understand clearance requirements and inform them about the shipment • Pre-clearance activities help streamline the customs process and identify potential issues in advance • Additional transparency and responsiveness can be achieved by better integrating customs into the end-to-end process and minimizing their workload through diligent shipment preparation and communication

It is important to recognize that precision therapies are continuously progressing given their potential and versatility within the field of healthcare, affecting logistics due to changing product and supply chain requirements.

Experimental techniques like the use of specific hydrogels to reduce product temperature sensitivity would reduce cooling and temperature control needs. Off-the-shelf allogeneic therapies show promise over their autologous counterparts with improved supply chain efficiency, responsiveness and scalability. Interest is growing in cutting-edge therapy types such as in vivo CAR T-cell therapies, which genetically modify immune cells directly in the patient's body, addressing challenges of current CAR T-cell treatments.[13]
Nonetheless, the focus areas identified in the logistics framework will remain essential for the distribution of these therapies, even as this field continues to evolve.

3. INDUSTRY INSIGHTS

PTL Survey

The survey results reveal three trends:
• Respondents agree that ATMPs and RLTs hold significant promise in treating rare and life-threatening conditions.
• Precision therapies cannot be handled similarly as traditional medication due to their stringent handling and distribution requirements. As a result, bespoke logistics processes are required to ensure their safe delivery.
• Despite their potential and the need for new logistics practices, the industry may lack the necessary standards and capabilities. This is illustrated by the final statement, where the respondents agree that airports, for example, may not always possess the correct competencies and/or infrastructure to correctly handle ATMP and RLTs.

Interviews and Workshops

Complementary to the survey, interviews were conducted with survey respondents and Pharma.Aero members to delve deeper into the acquired results and obtain a multidisciplinary perspective on precision therapy logistics. Thereafter, two workshops were organized with Pharma.Aero members, one virtual and the other during the Pharma Logistics Masterclass in Dallas. These workshops led to a comprehensive understanding of an ideal shipping lane and its critical success factors, laying the groundwork for the logistics framework.

> "One error and the entire shipment had to be scrapped.
>
> **The need for perfection**

> "Every single risk and its potential impact had to be assessed.
>
> **Lane mapping**

> "Training extended beyond our 4 walls to ensure correct handling of these products.
>
> **Stakeholder training**

> "Decentralisation is key to meet future demand.
>
> **Scalability**

13 Mullard, A. (2024) Nature: https://www.nature.com/articles/d41573-024-00150-z

• In summary, the different stakeholders emphasize a consensus on the need for a new logistics plan.
• To improve the speed and safety of ATMP or RLT shipments, the implementation of a standardized label is crucial to signal their criticality.
• Efficient customs clearance continues to be a major challenge, partly due to the lack of specific product codes.
• Extensive operator training is essential to prevent potential delays and ensure quick responses to deviations.
• Misalignments occur when shippers provide incomplete or inaccurate logistics needs.

The need for perfection

• There is no harmonized end-to-end process yet for these therapies
• Visibility platforms and SOPs are critical to have a clear view on the different stakeholders, their responsibilities, liabilities and performance
• Production needs to be closer to the patient to ensure future scalability
• Opportunities are being pursued to safely handle therapies at higher temperatures to reduce logistics complexity and costs

Airlines and airports

• Wrong product codes at the time of shipment booking are a common pitfall
• There is a need for a specific shipping label indicating the product type, handling constraints and priority status
• Coordination with ground handlers is key to ensure the right equipment and facilities are available to (un)load and store the products
• Customs clearance at the destination is often a significant hurdle

Logistics service providers

• Shipment success often depends on complete documentation and the timely communication of logistics requirements
• A frequent issue is the efficient pick-up and drop-off at hospitals
• Customs may sometimes be perceived as a “black box” with little visibility
• Responsibilities are driven by the agreed-upon Incoterms

Packaging and visibility providers

• Just-in-time delivery of packaging can be challenging, but critical as the packaging is validated for a certain duration
• There is a higher need of real-time visibility to enable proactive interventions
• Redundancy and communication plans must be in place, for example to re-ice the shipment in case the duration is longer than foreseen
• Training and certifications are key when dealing with dangerous goods such as dry ice or liquid nitrogen

CONCLUSION

Precision therapies like ATMPs and RLTs offer a revolutionary approach to relieve patients from complex, rare and severe conditions, and will only become more prevalent in medical treatment. However, these therapies require bespoke logistics processes to reach patients, given their stringent product and supply chain requirements. Neglecting logistics during therapy development can cause serious issues such as failure to meet lead time requirements or prevent quality issues, potentially jeopardizing patient safety. The therapies are just leaving the pipeline in a high sequence, and the applicability of such therapies are still in development which might introduce more and new indications therapies on the one hand, and might also introduce newer and adapted preservation technologies on the other hand. Consequently, Pharma.Aero's PTL project set out to explore the handling and distribution requirements of these therapies to construct a logistics framework that ensures safe, secure and effective distribution. These insights were gained through desk research complemented by an industry survey, interviews and workshops. Although initially planned, pilot shipments were excluded due to their excessive complexity for this project phase.

The logistics framework, which identified eight interconnected focus areas, demonstrates that integrating people, processes and technology is essential for delivering precision therapies. Certified and trained personnel follow clear processes to ensure the correct handling of products and to resolve issues along the supply chain. Dedicated teams and collaborative technologies guarantee end-to-end coordination and proactively manage common challenges like customs clearance and temperature control.

Pharma.Aero's Precision Therapy logistics project lays a solid foundation for the next phase of the PTL Excellence Gateway project. The framework will be further tested and expanded by developing a shipping protocol, standardized shipping label, and conducting pilot shipments with different stakeholders and industry partners. These harmonization efforts in logistics will continue to drive the success and accessibility of ATMPs and RLTs, ultimately benefiting patients worldwide.

Pharma.Aero VZW
Bedrijvenzone Machelen Cargo 706B
(mailbox 92)
4th floor, room 411
B - 1830 Machelen
Belgium

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