White Paper

Pharma’s Frozen Assets

Cold chain medicines

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Introduction

A huge and lingering logistical challenge in delivering vaccines globally during the pandemic has been in scaling up the refrigerated networks that make up part of the global “cold chain” — the uninterrupted process of maintaining end-to-end temperature-controlled conditions from the manufacturing site to the point of care. Cold chain medicines require more energy than their ambient temperature counterparts. If pharmaceutical companies want to live up to their ambitious environmental, social and governance (ESG) targets, they will need to understand current and future trends and work closely with logistics companies to ensure delivery of often live-saving cold chain medicines whilst having their CO_2 footprint in mind.

Healthcare is contributing an estimated 4.2% of the global carbon footprint.[1] The share of pharmaceuticals is significant. Studies conducted in the UK and France report medicines’ share of total health systems’ emission to be 25% and 33% respectively.[2,3] As part of environmental, social and governance (ESG) goals, pharma wants to become greener. In addition to reaching environmental targets, the recent sharp rise in gas prices and resulting high inflation make saving energy also an economic imperative. Natural gas prices increased by 139% in the first half of 2022 compared to the previous year.[4] Pharma manufacturers face a 400–500% and 100-200% rise in costs for shipping containers and some API precursors, respectively.[5]

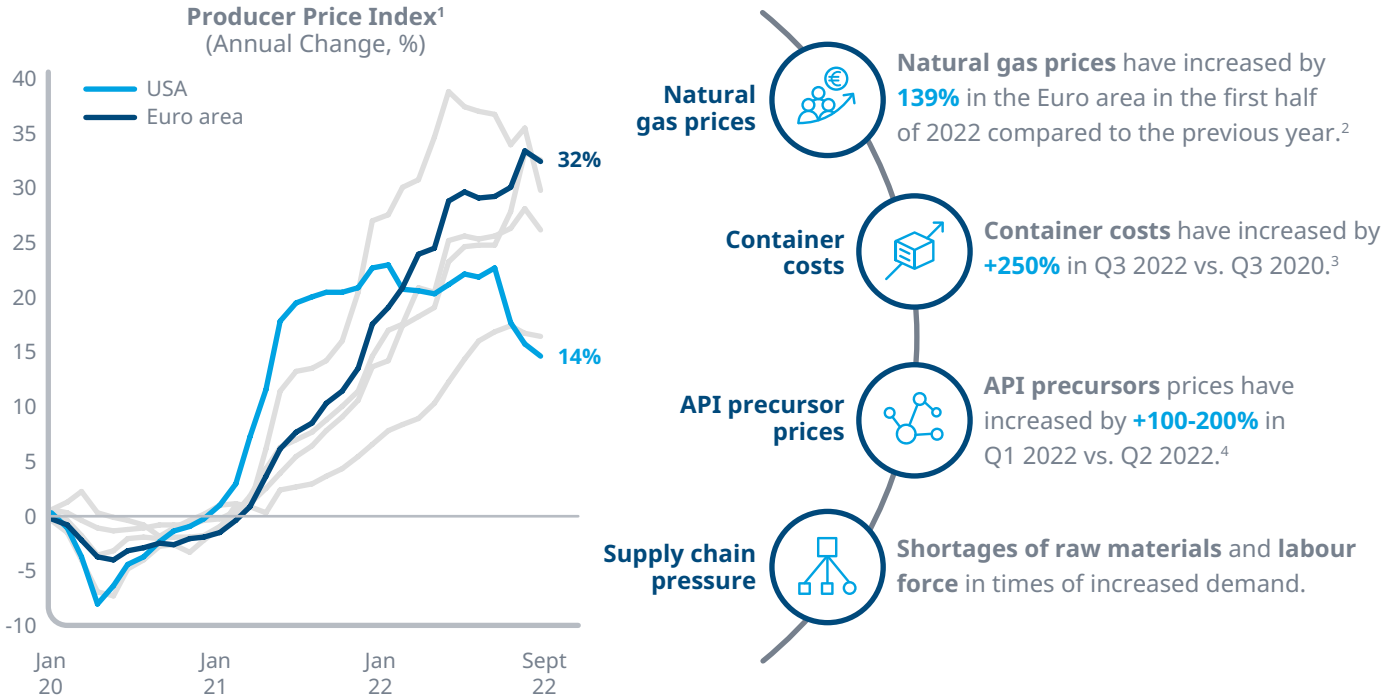
As a result, the annual producer price index, inflation measured from the producers' perspective, is up by 32% in the Euro area in September 2022.[6] Shortages of healthcare workers and increased demand for pharmaceuticals as healthcare system recover from the acute phase of the COVID-19 pandemic further exacerbate the situation (Figure 1).

Global rollout of the unprecedentedly fast development of the novel mRNA-based COVID-19 vaccines in 2021 brought additional challenges for the pharmaceutical supply chain as they required ultra-low temperature freezers that can reach -80 degrees Celsius for long-term storage. Wholesalers, pharmacies, HCPs and vaccination centres around the globe had to quickly scale up and invest in the refrigerated network that makes up the pharmaceutical "cold chain". The cold chain is the term given to an uninterrupted temperature-controlled supply chain that encapsulates production, storage and distribution to maintain quality and safety from bench to bedside. Vaccines, and many biologics — including insulins — are often considered the most common cold chain drugs.[7] Biologics consist of complex combinations of amino acids, nucleic acids or sugars that are produced by a variety of biotechnological processes. Cooling is required to avoid contamination with bacteria and formation of potentially harmful protein aggregates. In contrast, most small molecules can be stored at ambient temperatures.

Refrigerated or frozen medicines have a more energy-intensive lifecycle from manufacturing until they reach the patients. Biologics and advanced medicinal therapy products (ATMPs) in high-income countries and vaccines in middle- and low-income countries will continue to drive cold chain medicine value and volume growth respectively. A looming recession and continuously high energy costs will likely lead to future economic austerity measures and consequently also impact healthcare budgets. Thus, pharma and their logistics partner need to investigate the highly specialised market of cold chain medicines to understand both their economic and environmental impact on their businesses.

Here we present a data-driven approach to assess volume and value of cold chain medicines by combining IQVIA audit data with publicly available data.

Figure 1: Macroeconomic factors impact the supply chain of pharmaceutical companies



Source: IQVIA EMEA Thought Leadership; (1) Eurostat, OECD; (2) Eurostat NRG_PC_203; (3) https://www.statista.com/statistics/1250636/global-container-freight-index/; (4) European generics manufacturer.

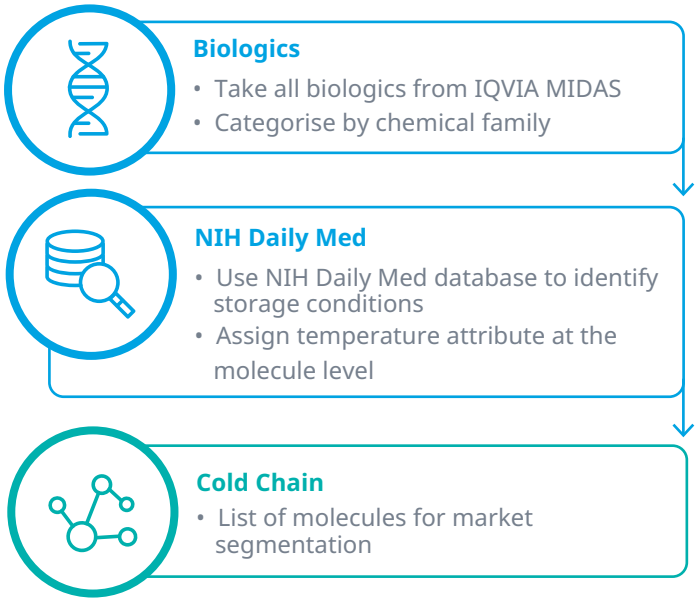
Approach to defining cold chain medicines

The information on which medicines require a temperature-controlled environment is not easy to come by. Cold chain medicines have not been explicitly annotated in IQVIA's MIDAS audit data. Therefore, we had to develop a new approach to infer cold chain requirements. Figure 2 describes the workflow that was used to identify cold chain medicines. We first used MIDAS' biologics definition and further split them according to their chemical family. Vaccines and COVID-19 therapeutics were excluded as MIDAS audits have low coverage for products that do not pass-through standard distribution channels.

Next, we used the public NIH Daily Med database section 16 "How supplied/storage and handling" to identify storage conditions at the molecule level to get a final list of 564 substances that have a cold chain requirement. Examples of biologics and their temperature requirements can be seen in Figure 2 right panel.

Figure 2: Definition and methodology of cold chain medicines

Workflow



Temperature Ranges

TEMPERATURE	DEGREE CELSIUS	EXAMPLES
Ambient	15-25	*Heparins*
Refrigerated	2-8	*Monoclonal Antibodies*
Frozen	Below -15	*mRNA Vx, Cell Tx*

Daily Med Section 16:
"How supplied/storage and handling"

Source: IQVIA EMEA Thought Leadership; https://dailymed.nlm.nih.gov/dailymed/index.cfm
Notes: Vaccines and COVID-Tx are excluded

The cold chain is the term given to an uninterrupted temperature-controlled supply chain that encapsulates production, storage and distribution to maintain quality and safety from bench to bedside.

The cold chain market: a global overview

Applying the above methodology to MIDAS data for the full year of 2021 provided the first overview of the cold chain medicines market (Figure 3). The total pharmaceutical market in 2021 – exclusive of vaccines and COVID-19 therapeutics – was almost $1.2 trillion out of which cold chain medicines made up $384 billion or 32%. High-value specialty indications immunology and oncology lead in first and second place directly followed by antidiabetics and collectively accounted for almost three quarters of global cold chain value. 98% of all specialty medicines that required refrigeration were patent protected. The eight major markets — US, EU4+UK, Japan and China — made up 83% of global cold chain medicines at list price sales.

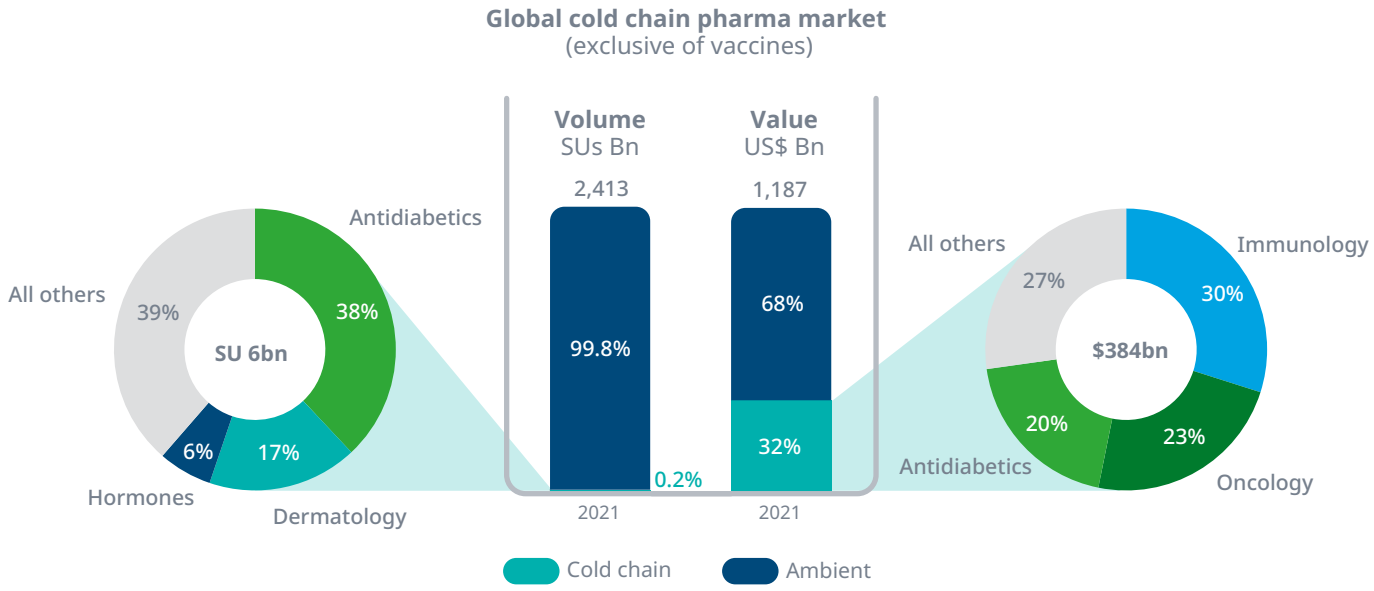
In contrast, cold chain volume was low at 0.2% of the global market of 2,413 billion standard units. The three therapeutic areas antidiabetics, dermatology and hormones together accounted for 61% of cold chain volume. High and in some cases exceptionally high value biologics were responsible for the overall value-volume gap. Insulins, Interferon Alfa-2B-containing sprays and desmopressin-containing drugs accounted for the discrepancy between value and volume in

Cold chain medicines grew more than twice as fast at 13% compared to 6% for the total market between 2017 and 2022.

antidiabetics, dermatology and hormones respectively. China and other emerging countries recorded 55% of globally sold refrigerated drugs by standard units.

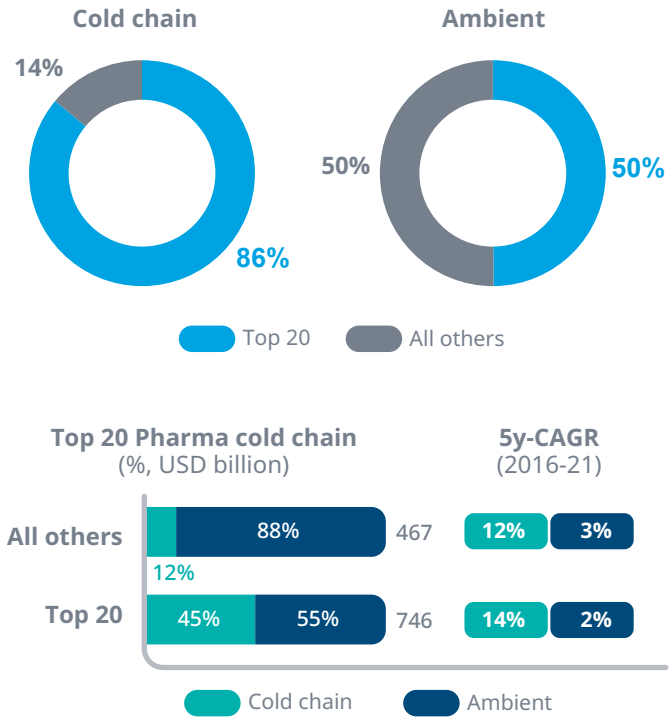
The 20 largest pharmaceutical companies by value account for 86% of sales of cold chain medicines in 2021. In contrast, their share is only 50% for ambient temperature substances. Moreover, 45% of top 20 pharma sales result from medicines that require refrigeration, and this segment was also growing faster than their ambient counterparts at 14% vs. 2% respectively (Figure 4). The proportional share of cold chain medicines of top 20 pharma has increased by 10% in the past five years.

Figure 3: Global cold chain market exclusive of vaccines and COVID-19 therapeutics



Source: IQVIA EMEA Thought Leadership; IQVIA MIDAS MAT Q4 2021; Rx-only; IQVIA Analytics Link; Global Medicine and Spending Trends - Outlook to 2026. Report by the IQVIA Institute for Human Data Science.

Figure 4: Top 20 pharma contribution to cold chain medicines

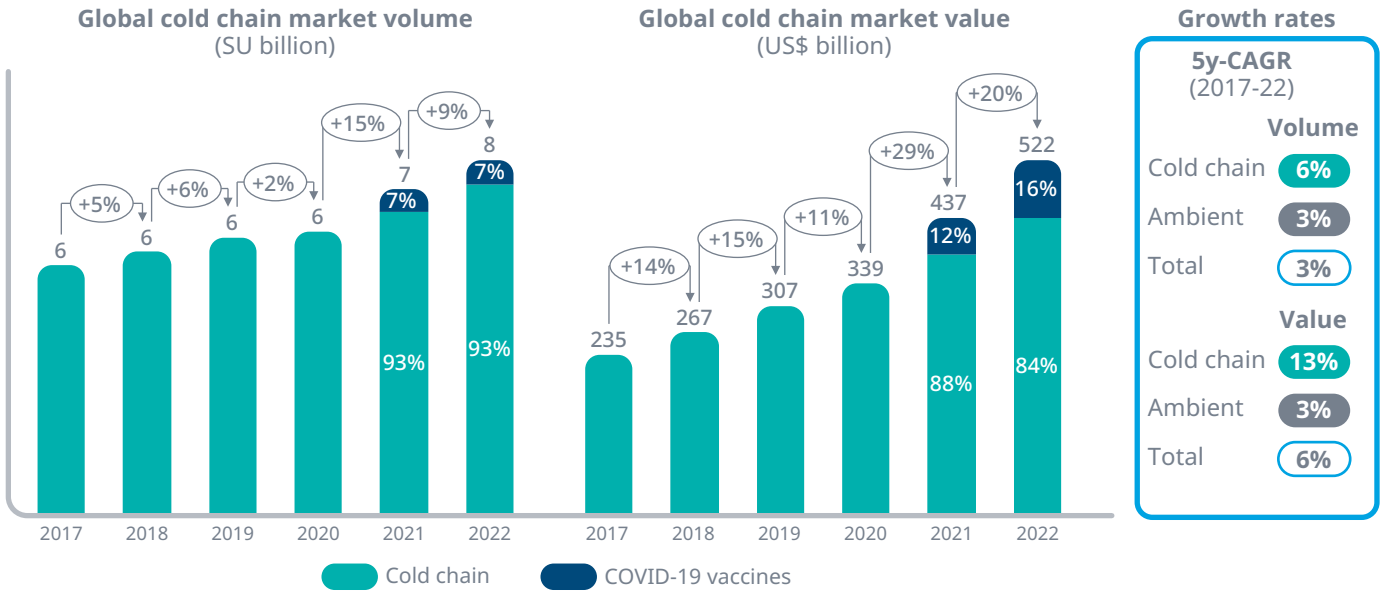


Source: IQVIA EMEA Thought Leadership; IQVIA MIDAS MAT Q4 2021; Rx-only; exclusive of vaccines.

Historically, the global volume of medicines has been growing at around 3–4% annually. As countries went into lockdowns and healthcare systems focussed all their resources to fight the COVID-19 pandemic, global volume growth came to a stop in 2020. Cold chain medicines were affected as well, as growth slowed down to 2% in absolute volume year-over-year (Figure 5 left panel). Medicines that are used in routine care including anti-coagulants were amongst the most affected substances. In 2021, global Rx volume grew at 4% as healthcare systems shifted their focus to address patient backlogs from missed diagnoses and the return of elective procedures. Cold chain medicines grew with 15%, and anti-diabetics in particular were driving the volume growth in 2021.

Cold chain medicines grew more than twice as fast at 13% compared to 6% for the total market between 2017 and 2022. In the same period, their market share increased from 26% to 35%. In contrast, ambient temperature medicines only grew 3% at the same time (Figure 5). The pharmaceutical cold chain was also resilient towards the pandemic with double-digit value growth rates at 29% and 20% for 2021 and 2022 respectively. Biologics in immunology, oncology and diabetes drove both short- and long-term value growth.

Figure 5: Cold chain medicines market development



Source: IQVIA EMEA Thought Leadership; IQVIA MIDAS MAT Q3 2022; Rx-only; Our World in Data; Company Financial Reports.
Notes: Exclusive of vaccines except for COVID-19.

Biologics have been a key growth driver over the last decade. This will likely continue as biologics represent 49% of the global pipeline.[9] Loss of exclusivity and measures to increase biosimilar usage in high-income countries will increase their uptake.

VACCINES – A HIGH-VOLUME COLD CHAIN MARKET

Collecting vaccine market information is challenging, and one of the most comprehensive sources available is the WHO which gathers information directly from its member states and estimates a total of 5.5 billion doses for 2019 but excluding the travel and military markets.[10] Based on the route of administration and formulation, we estimate the WHO numbers to be equivalent to 2–2.5 billion additional standard units added to our cold chain medicines number. The WHO values the total vaccines market at $33 billion in 2019. Global efforts on the reporting of COVID-19 vaccine rollouts across the globe enabled us to estimate their impact on the 2021 cold chain medicines market more accurately.[11] Value calculations were based on vaccine sales from company quarterly reports for Comirnaty, Spikevax, Vaxzevria, Spikevax and J&J vaccine. Volume calculations in standard units (SUs) were based on figures from Our World in Data (OWID) on total vaccine doses administered at a country level, and an average doses per pack based on approved vaccines in each country as of May 2022. This resulted in an addition of 490 million SUs and $54 billion in 2021 and 555 million SUs and $85 billion in 2022 (Figure 5).

Respiratory vaccines benefited in the early phase of the COVID-19 pandemic as people were more aware of other threats to their health. In contrast, routine immunisation campaigns and travel vaccines were negatively affected. The WHO already warned about a rise of vaccine-preventable diseases (VPD) cases in early 2022.[12] Heightened public awareness, new vaccine launches against e.g., respiratory syncytial virus (RSV) and global efforts to continue vaccination programs against VPD will be the driving forces in the future.

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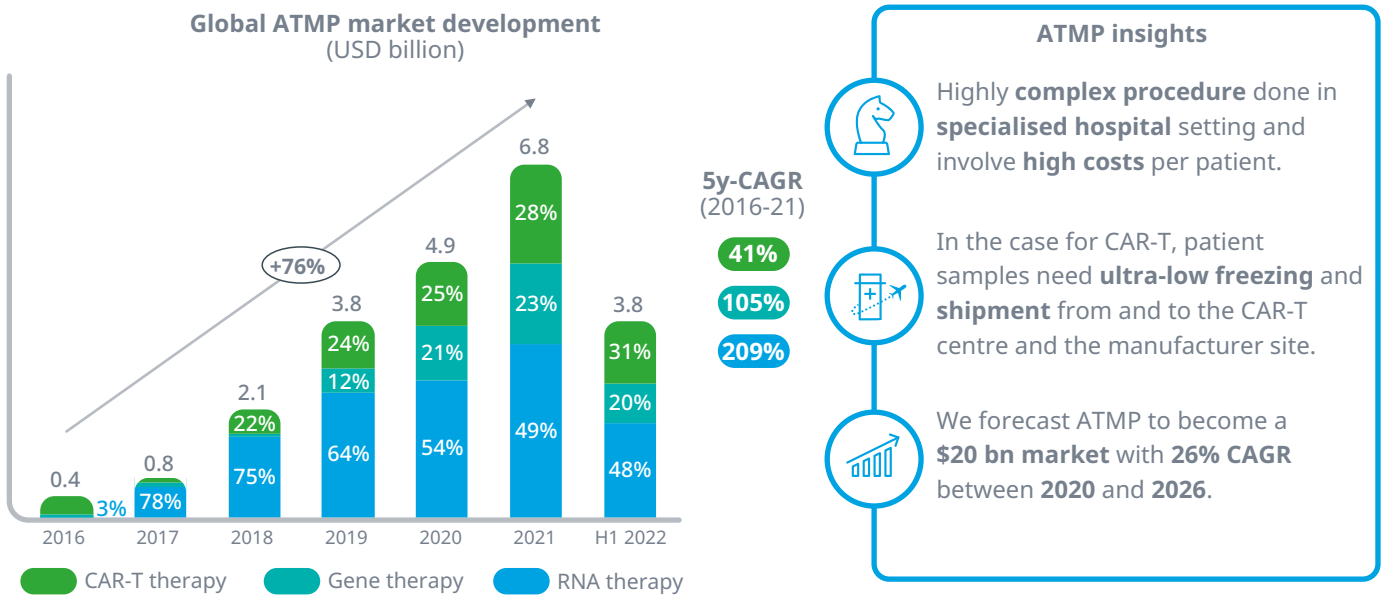
Figure 6: Global ATMP market development



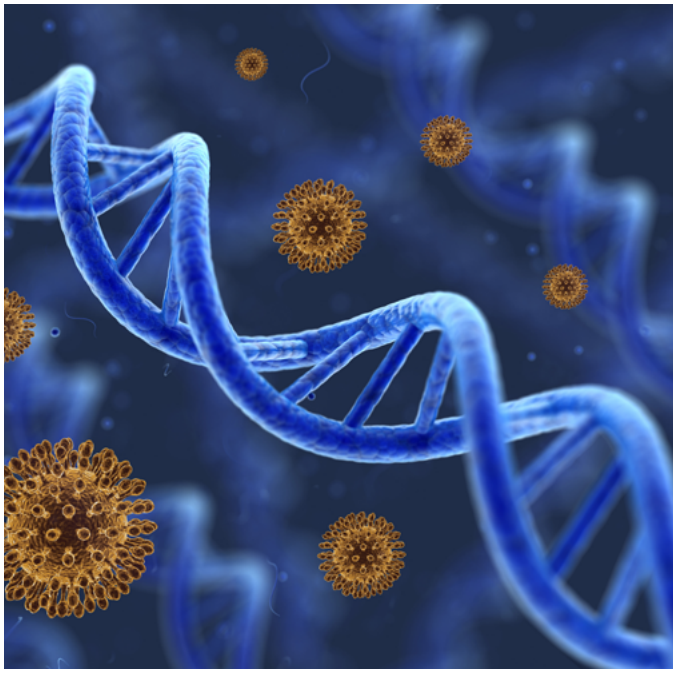
Source: IQVIA EMEA Thought Leadership; IQVIA MIDAS MAT Q2 2022 and Company Financial Statements.

LOGISTICAL CHALLENGES AROUND NEXT-GENERATION BIOTHERAPEUTICS

Advanced therapy medicinal products (ATMPs) are collectively defined as a class of highly-innovative novel drugs or procedures that require complex logistics – including refrigeration and sometimes even temperatures below -120 degree Celsius. Patient-derived (autologous) CAR-T-cell therapies are a case in point. T-cells must be extracted in a process called leukapheresis, subsequently cryo-frozen, shipped to the manufacturer's site and then back to the CAR-T centre where the modified cells are administered to the same patient. CAR-T, gene and RNA therapies are now big business, with billions of dollars of sales and considerable investment by pharmaceutical companies, ranging from the top ten to emerging biopharma.[13] The ATMP market has grown by +76% CAGR from 2016–2021 and reached $6.8 billion in 2021 (Figure 6).

Gene and RNA therapies accounted for 23% and 49% of the ATMP market respectively in 2021. The current focus for those two classes of therapies is for (ultra-) rare diseases and sales are dominated by few products on the market. The IQVIA Institute expects ATMPs to become a Top 20 medicines market valued at $20 billion by 2026.[14] RNA therapeutics are expected to contribute the largest share of this value, ahead of (CAR-T) cell therapies then gene therapies.

The logistics around CAR-T therapies will stay challenging in the near-term future. Manufacturers, HCPs at the point of care and logistics companies need to work closely together to ensure proper sample handling – including end-to-end cold chain integrity. Issues might result in worse treatment outcomes or even complete failure. In 2021, Spain approved the first European-developed CAR-T cell therapy that can be produced and administered directly in the hospital[15]; thus, eliminating the need for sample transportation altogether.



Implications for pharma and logistics companies

Pharma and their logistics' partners ship their products by sea or air freight using active (energy/battery-powered) and passive (insulating materials, refrigerants or phase-change materials) cooling solutions. End-to-end cold chain compliance is a regulatory requirement and, if broken, leads to economic damage or worse, patients' health could be at risk. Whilst avoiding temperature excursion works well during the first and longest leg of transportation, issues more frequently occur during the last stage of the supply chain – the last mile delivery. At this step, cold chain medicines are transported in less well temperature-controlled environments and temperature fluctuations might happen. The extent of the last mile challenge varies depending on the product. For example, up to 50% of global vaccines are wasted due to failures in the cold chain according to the WHO. The number probably being even higher in poorer countries. Challenges around vaccine cold-chain logistics remain especially acute and are twofold: 1. They are high volume products and 2. need to reach even the most isolated and of often very poor populations. In other words, low-income countries without sophisticated cooling infrastructure. In contrast, the complex logistics of high value/low volume ATMPs are a challenge of high-income countries.

There is undoubtedly a clear need to improve the logistics of pharmaceutical cold chain to avoid e.g., discarding expensive medicines or, if possible, to minimise or even avoid refrigeration altogether. Measures how this can be achieved are outlined below.

Fast development, distribution and access to life-saving vaccines was critical in our fight against COVID-19. The latter is still an issue today and one that is further exacerbated by stringent cold chain requirements. Manufacturing vaccines closer to where they are needed reduces transport time and thus facilitating e.g., the switch from active to passive cooling. BioNTech aims to bring its mRNA-based vaccines closer to customers in sub-Saharan Africa. The company's modular container manufacturing solution enables state-of-the-art vaccine production of its COVID-19 vaccine and investigational malaria and tuberculosis vaccines.[16] At the same time also improving access to vaccines in general. Africa's population is equivalent to 16.2% of the total world population but only produces 0.1% of the global supply of vaccines.[17] Going forward, this imbalance must be rectified to fight present and future infectious disease outbreaks.

The initial -80°C to -60°C ultra-low temperature storage requirement of the COVID-19 mRNA vaccines was a challenge to their fast distribution across the world, especially in countries with less developed infrastructure. Based on stability data, storage of the vaccine in standard freezers for two weeks was approved by the EMA in March 2021.[18] According to CDC guidelines based on manufacturer data, both the Moderna and BioNtech/Pfizer jab can now be stored at 2°C to 8°C for four and ten weeks, respectively.[19,20] Even before the pandemic, scientists and companies were working towards vaccines that could ditch the fridge. A temperature stable freeze-fried smallpox vaccines was essential to eradicate the disease and scientists are optimistic that advances around

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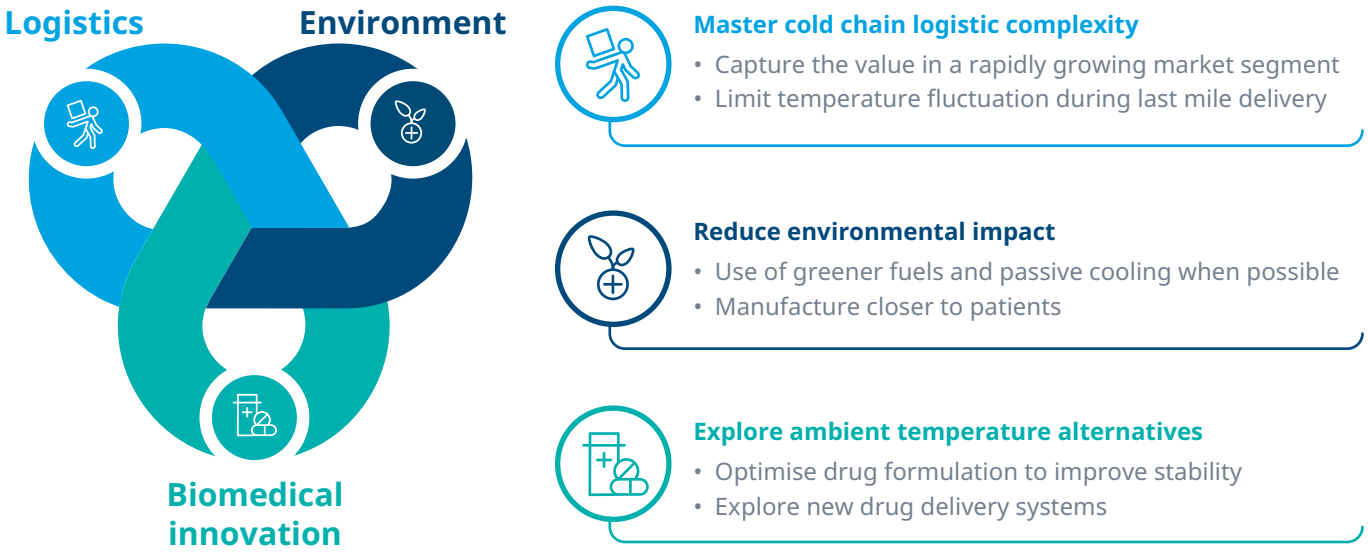
Figure 7: Considerations for pharma and logistics companies



Source: IQVIA EMEA Thought Leadership.

novel technologies or improved formulation will make ambient temperature stable vaccines a reality 10 years from now.[21] Stablepharma's fridge-free vaccines aims to dramatically enhance the stability of existing and new vaccines, thereby expanding access to patients and increasing the success of immunisation programmes.[22]

Optimisation of formulations can improve shelf life, enable self/home administration and reduce the cold chain burden of non-vaccine biologic products as well. Ease of use has been a focus area of the industry. Particularly to manage chronic conditions with single use injectables in immunology indications. To mitigate environmental concerns such as reducing waste and carbon emissions, the industry will need to focus on innovation around reusable devices.

Transdermal drug delivery systems combine continuous drug delivery with patient convenience and can be stored at ambient temperatures. Amongst the most prominent examples are nicotine patches that aid in smoking cessation therapy or transdermal patches designed to treat chronic pain. Whilst transdermal patches are limited to small molecule drugs, modern microneedle patch technology can also deliver vaccines and biologics, thus eliminating the cold chain and associated costs and challenges. Vaxxess Technologies recently announced phase 1 clinical results demonstrating that their delivery patch induced an immune response exceeding the 2007 FDA criteria for accelerated licensure of influenza vaccines.[23] Nasal and/or inhaled vaccines are also entering the spotlight. CanSino recently gained the first approval for an inhaled COVID vaccine in China.[24] CanSino's Convidecia Air still requires refrigeration, but nonetheless has lower cold chain requirements, making it more accessible than its frozen mRNA counterparts. Patches, nasal or inhaled vaccine administration eliminate the use of needles and associated issues altogether and could improve vaccine uptake in the future.

The majority of CO_2 emissions occur during pharmaceutical manufacturing whilst logistics – including the cold chain – is responsible for a smaller but not negligeable share. The exact impact of the cold chain on pharma's CO_2 footprint itself is hard to measure but likely has a significant impact on the environment. Trucks need to carry refrigeration units to ensure controlled temperatures and produce 8 tonnes of CO_2 a year – equal to four average cars in the UK.[25] Pharma companies will need to address the cold chain's impact on the path towards net zero emissions. The usage of greener fuels is one way to reduce their carbon footprint. Recyclable active cooling containers can help to lower CO_2 emissions significantly.[26] Using less packaging material makes better use of available space during transport and, for example, helped Johnson & Johnson reduce the total number of vehicles required.[27]

Conclusion

The sustained growth of the cold chain medicine market, which outperformed the ambient segment, poses profound logistical challenges for manufacturers and health system. Maintaining end-to-end cold chain integrity is paramount for success in this market segment.

Given the energy-intensity of the cold chain, medicines that rely on it are a contributor to the significant, overall carbon footprint of healthcare systems and that of the respective manufacturer. Reducing that carbon footprint will be critical in pursuit of net-zero ambitions, for example, by deploying more efficient logistics solutions, using greener fuels or minimising the need for a cold chain in the first place, for example, by localising manufacturing or developing novel formulations that are stable at ambient temperature.

Undoubtedly, supply chain innovation must go hand in hand with biomedical innovation.

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