Pharma Logistics IQ

Safety and Sustainability in the Global ATMP Market

Reliable Temperature Control for Advanced Therapy Medical Products (ATMPs) is Vital for the Growth of this Industry

By Nicholas Basta

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CONTENTS

Nicholas Basta is the founder and former editor-in-chief of *Pharmaceutical Commerce*, a publication that focuses on commercial activities in the biopharmaceutical industry.

It's boom times for businesses involved in the biopharmaceutical cold chain, from freezers inside labs and production units to the single-dose packages delivered to patients' homes or hospital infusion centers. Coming off the ramp-up for delivering billions of dosages globally for the Covid-19 pandemic (which required shipping refrigerated or ultra-frozen dosages), the logistics, packaging and data-tracking companies are at a new, higher plateau of capability, and the biopharma industry wants all those capabilities and more.

The numbers are staggering. The Alliance for Regenerative Medicine (ARM), one of the leading trade associations in the field, counted $23.1 billion of investments in the field in 2021—up 16% over the year before. "Unprecedented access to capital in the private and public markets has fueled this progress," commented Jason Rhodes, partner at the financial firm Atlas Ventures, in ARM's 2022 annual report. Over 1,000 companies are engaged globally, and that doesn't count the thousands of academic researchers investigating new cell lines, new genetic manipulations and the like. Over 2,200 clinical trials are being conducted, and of those 216 are in Phase III. FDA expects 10 to 20 newly approved therapies per year for the next several years, representing perhaps a third of the approvals of any type of new molecular entities.

Behind these eye-popping numbers is a nearly frantic race to keep up with the new science and new discoveries. Arguably, the race started when the Human Genome Project was completed around the year 2000. In more recent years, technologies like CAR-T (chimeric antigen receptor-T cell) and CRISPER (Clustered Regularly Interspaced Short Palindromic Repeats) have opened up new avenues for how to identify, modify and apply the therapies.

Putting all the molecular genetics and cellular mechanics to the side, there are two important concepts to keep in mind when thinking about how these wonder therapies will reach patients: first, for the most part they involve living cells (sometimes, viruses); second, this living matter needs precise temperature control (often in cryogenic ranges) to remain viable and potent. A new infrastructure to monitor and record those storage and shipping conditions is being created as you read these words.

"It is important to focus on a proactive response to temperature deviations, and share relevant information with the ecosystem, such as customers, internal stakeholders, and health authorities," says Ruud van der Geer, Associate Director, Global Delivery, MSD, who will be speaking at the **Temperature Controlled Logistics & Security U.S. Summit (Philadelphia, Nov. 1-3, 2022).**

Some Definitions

It's worthwhile to take a moment to understand what these new therapies are, and what challenges they represent to industry and healthcare. In the US in the 1990s, the concept of "regenerative medicine"—repairing or growing body organs with living tissue became a topic of intense clinical development. Along the way, the isolation (in 1998) of embryonic stem cells opened up a much broader world of using human cells in therapeutic applications. That, plus other discoveries, led to today's classification of CGTs. (The Alliance for Regenerative Medicine, while covering the CGT space extensively, also includes "tissue engineering," which harkens back to the "regenerative" sense of this science.)

In Europe and elsewhere, the concept of ATMPs (Advanced Therapy Medicinal Products) was arrived at as a way to encompass CGTs, regenerative medicine and, frankly, whatever other new stuff comes up. Meanwhile, within the US Food and Drug Administration, the RMAT (Regenerative Medicine Advanced Therapy) designation came into being under the 2016 21st Century Cures Act. All these designations are important because regulatory and review processes have been set up, in the US and elsewhere, specifically for these therapies. Some of the regulations allow for an accelerated review and approval process (not available to non-RMAT or -ATMP products); all of them call for extensive tests of purity and potency of not only the final product, but also the source materials like cells and viruses.

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Industry standards are the operational aspect of a regulation—there is a combination of mandatory and voluntary standards being developed, and regulators are scrambling to keep up with their ability to oversee these developments. In 2017, FDA assigned a group, the Standards Coordinating Body for Regenerative Medicine (SCB for short) to draw together literally dozens of other standards-setters to establish common practices.

This standards-setting process is ongoing; there's almost a hopscotch occurring between a new type of research appearing, and a new standard practice being proposed as clinical development occurs. Within the past year, ARM issued Project A-Gene, a "multistakeholder collaboration to incorporate Quality by Design (QbD) principles into a manufacturing case study of a viral vector commonly used in gene therapies." The effort follows previous similar projects, A-Mab and A-Vax, to establish

common practices for quality in (respectively) monoclonal antibody and vaccine production. “Each of those technologies faced similar hurdles when developers sought to advance from small-batch manufacturing for clinical trials to full-scale commercial production,” said the organization.

More specific to supply chain issues in ATMPs, the International Standards Organization issued ISO 21973:2020, Biotechnology—General Requirements for Transportation of Cells for Therapeutic Use. “Issues related to cell transportation … include monitoring and controlling transportation conditions, managing traceability and maintaining chain of custody, and establishing clear expectations and communications between cell product manufacturer and transportation service provider.” (The actual text is available for purchase from iso.org.)

Cryoport, a leading provider of supply chain solutions for life sciences, calls ISO 21973 “a leap forward” for the industry, noting that “In a global environment, the specification and diligence in the packaging and transportation of these therapies varies significantly, resulting in considerable risk and potential loss of irreplaceable therapies.”

The pharma cold chain, of course, long preceded the advent of ATMPs—its origins can be traced back to the introduction of animal-derived vaccines and insulin in the early 1900s. By the 21st century, a large and growing array of logistics, packaging and pharmaceutical guidances have been issued, by organizations ranging from the International Safe Transit Assn. (for air freight) to the Parenteral Drug Assn. (for injectable pharmaceuticals). A key effort—continuing now—is the efforts of US Pharmacopeia (USP), which has a quasi-regulatory status for food and healthcare products. Currently, there is a program to update a group of guidances known as General Chapter <1079>, with topics ranging from storage and transportation of investigational drug products, qualification of storage areas and shipping systems, and transportation route profiling, among others.

Vein to Vein

While there are almost as many distinct processes to delivering an ATMP therapy as there are therapies themselves, perhaps the most

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illustrative example of ATMP challenges is with autologous cellular therapies—about a dozen of which are now commercial. In these cases, the process starts with an extraction of the patient's own cells (typically, T-cells) by apheresis, then routing the cells to a lab/manufacturing facility where the cells are treated or manipulated genetically and "expanded" (grown). Then the cells—usually stored under cryogenic conditions—are sent back to the facility where the patient is, to be infused. Thus, so-called "vein-to-vein" therapy. Careful monitoring of the infusion step is necessary because this step can be life-threatening to the patient…

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