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Allogeneic Therapies: Can This be the Silver Bullet for All Future Cell Therapy Developers?

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The burgeoning cell and gene therapy (CGT) industry has seen 6 CAR- T cell therapies win commercial approval in the US and the FDA has predicted 10–20 new CGT approvals per year by 2025 [1]. While all the commercially approved T cell therapies today are autologous, the industry is buzzing over the doors that allogeneic cell-based therapies have the potential to open.

The 'Off-the-Shelf' Promise

Allogeneic therapies have the potential to disrupt the industry by bringing cell therapies straight to the shelves of clinic stock rooms, significantly reducing the burden of what is currently a lengthy, made-to-order production cycle for autologous therapies. Today, there are ~250 allogeneic genetically modified cell therapy products being investigated globally [2], which accounts for 16% of the overall cell therapy market. These include products such as CAR-NK, CAR-T, TCR-T, CAR-M and gamma-delta T cell therapies, to name a few.

Autologous therapies require the patient to undergo an initial cell collection that becomes the biological starting material for that specific patient. On the other hand, allogeneic therapies are manufactured from 'healthy donor' cells (See Figure 1).

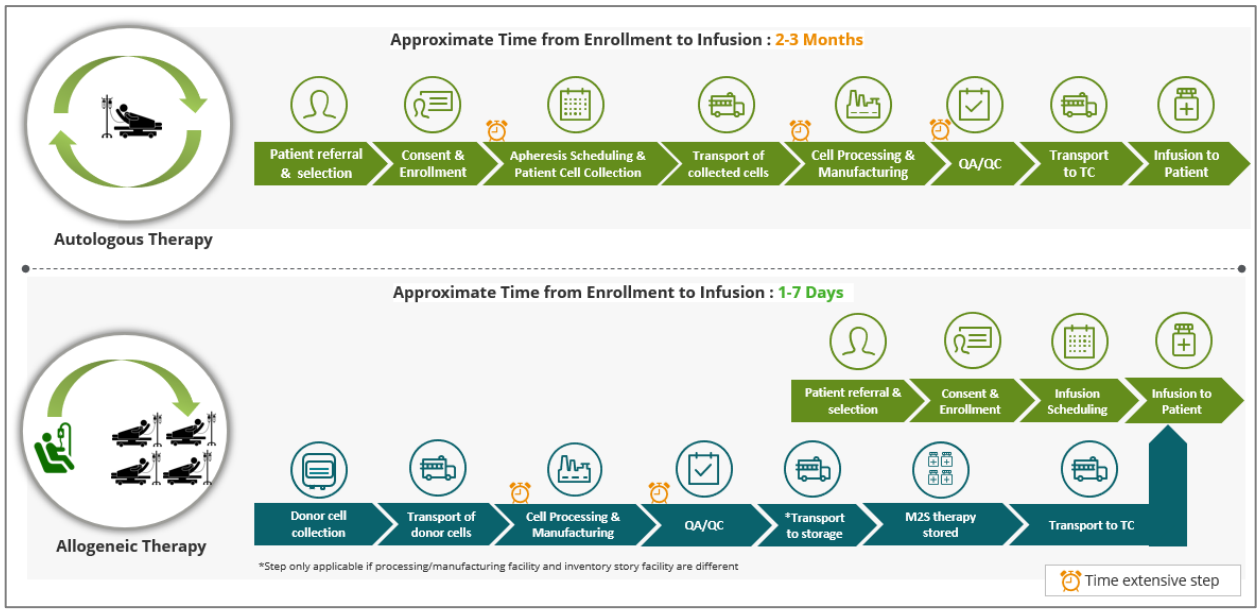

Figure 1: A high-level depiction of the comparative production cycles and timelines between typical autologous and allogeneic cell therapies

This key difference may vastly improve availability and patient accessibility while also reducing supply chain, manufacturing and quality control complexities. Some key opportunities that allogeneic therapies could afford include:

1. **SOURCING: Opportunity to select a high-grade starting material.** Cells sourced from healthy donors may serve as 'better quality' raw material, potentially driving higher manufacturing success, than autologous cells that have undergone multiple rounds of beatings from prior chemotherapy. Additionally, by targeting specific donors for apheresis collection, cells with certain characteristics (i.e., EBV negative, CMV negative, specific human leukocyte antigen (HLA) types, KIR-tested, etc.) can be sourced as starting material.

2. **MANUFACTURING: Opportunity to simplify the supply chain and reduce manufacturing costs.** Off-the-shelf convenience, less complex logistics, more standardized manufacturing processes, higher scalability, and reduced manufacturing costs per dose due to multiple lots derived from a single batch are some key advantages.

3. **LOGISTICS & DISTRIBUTION: Opportunity to expand access.** Scalable manufacturing, simplified distribution chain and reduced cost can simultaneously drive cell therapy prices down and accessibility up.

4. **PATIENT ACCESS & PROVIDER BURDEN: Opportunity to lower overall burden on patients, treatment centers, and manufacturers.** 'Bulk' manufacturing may allow for competitive pricing and addresses time-sensitivity challenges of coordinating patient apheresis, product processing, manufacturing, and infusion scheduling, all while sparing patients from cell collection procedure and financial burden.

Headwinds to Allogeneic Therapy Ecosystem Remain Persistent

Despite its enticing advantages, allogeneic modalities are still far from being a silver bullet. Some pressing challenges across the above opportunities include:

1. **SOURCING: Increased reliance on donor cells as raw material is proving to be a bottleneck.** Increased reliance on repeated donor collections requires access to extensive donor databases, stringent donor selection criteria and advanced screening and testing capabilities post-donation. Any slight variation in product quality has the potential to impact a much larger patient population since the production is one-to-many.

2. **MANUFACTURING: CMC and regulatory controls have not been well-defined**. Process efficiency and safety challenges have been prime reasons for recent clinical holds with request for potency assays prior to enrolling patients in efficacy trials or request for control data for genomic rearrangement ensuring limited to no off-target effects demonstrating lack of established guidelines manufacturers can follow. However, FDA's increasing understanding of the nuances of the relatively new cell therapy modalities imply resolution of these holds is observed within 3–6 months [3].

3. **LOGISTICS & DISTRIBUTION: Supply chain and distribution nuances may put a significant dent in the economies of scale for allogeneic therapies**. Whether to store the drug product in a highly controlled environment via a network of warehouses, or to build a highly flexible and speed-dial-ready courier system for quick on-demand delivery to a multitude of clinics remains an open question. Evaluation of drug product dosage formulation strategy within the warehouse also adds to the existing distribution complexity.

4. **PATIENT ACCESS & PROVIDER BURDEN: Clinical safety profile and the need for immunologic matching at scale is challenging.** Clinical concerns like alloreactive T cell induced graft versus host disease have forced developers to include some degree of donor to recipient matching (i.e., HLA-matching) or patient-specific production. This

'made-to-match' requirement reintroduces several of the same challenges currently facing autologous cell therapies.

Examples of recent clinical holds by the FDA bring forward critical questions facing the CGT industry around the challenges that allogeneic cell therapy companies may encounter as they make the leap from preclinical to clinical stage [4]. It is still early to say allogeneic therapies will truly offer 'made to stock' convenience or if safety issues and regulatory requirements will drive some level of personalized 'made to match' manufacturing, thus raising many of the same supply chain challenges facing autologous therapies today.

	Autologous Therapies	Allogeneic Therapies
Manufacturing	Centralized, single lot	Decentralized, batch production
Source of Cells	Patient's leukapheresis collection	Healthy Donor (Leukapheresis, cord blood, MNC cell bank or iPSC cells)
Opportunities to Scale	Scale-out	Scale-up
Distribution Model	One-to-one; made-to-order	One-to-many, made-to-stock or made-to-match
Treatment Timeline	Months	Days-weeks
Patient role	Cell collection and infusion	Only infusion
Patient convenience	Currently only in-patient treatment	High, option of out-patient infusion
Costs	Very High	20-30% lower than autologous therapies
Redosing	Based on availability of cells from previous batch (limited)	Possible if needed
Potential for communicable infection	Limited	Possibility exists
Safety Profile	Medium with high rate of Grade-3 AE, CRS and neurotoxicity	High, need for lower dose of immunosuppressants but risk of GvHD and HvGA exists

Figure 2: Comparison of the salient features of Autologous vs. Allogeneic adoptive cell therapies

If Not a Silver Bullet, There is a Silver Lining

Leaving the science and the clinical implications aside, the question that remains is – how do allogeneic cell therapy developers prepare themselves for commercial launch, and would we need an entirely new model for such products? The answer is no! Allogeneic therapies share several commonalities with traditional made-to-stock biologics and autologous cell therapy models. Based on our experience preparing launches for allogeneic therapy companies, we strongly believe that the industry would not need to 're-invent the wheel' here.

Allogeneic cell therapy manufacturers must consider 5 key commercial readiness attributes that are the building blocks for a successful commercial launch for first-in-class therapies.

- **Start with outlining your critical process journeys**
  - Clearly mapping out the donor, product and patient journeys should be one of the first steps – this serves as a blueprint for designing your supply chain strategy and processes. Additionally, this becomes the foundation for your digital orchestration engine that is typically needed to manage the manufacturing orders and patients.

- **Establish strong secondary supplier and manufacturing partnerships**
  - Strategic partnerships with critical raw material suppliers and vendors (CDMOs, CROs, apheresis collectors), are key to success for late clinical stage manufacturers. Ensuring secondary supplier relationships creates a supply safety-net but also allows manufacturers access to diverse and

customizable product offerings from highly characterized donor pools, which is essential to scaling commercial production.

- **Communicate early and often with your contracted suppliers and partners**
    - As allogeneic manufacturers prepare for their first commercial filing, early alignment with both primary and second suppliers and manufacturing partners around anticipated production volumes, shifting cGMP requirements and any regulatory agency feedback that impacts supplier materials or CDMO processes, is paramount to a smooth launch.

- **Identify and plan a robust logistics and distribution strategy**
    - Despite some clear supply chain advantages, allogeneic therapies also bring in the added complexity of cold chain logistics. A possibility of leveraging existing donor cell collection centers with cell processing capabilities as potential dose formulation centers could hedge expenses incurred in building / leasing large regulatory compliant warehouses. Developers should critically evaluate their storage and logistics readiness as they plan for commercial launch.

- **Initiate critical CMC assay development early as part of regulatory filing strategy**
    - FDA is focusing especially on the quality and production of cell therapy products and general CMC themes [5]. In light of the recent string of PDUFA delays and/or CRLs received by sponsors, it is critical to ensure characterization and potency assays are satisfactory to the agency and hence developers should ensure developing validated potency assays ahead of pivotal Phase II/III studies.

Catalyzed by the success of autologous CAR-T therapies, the adoptive cell therapy space is experiencing a renaissance that has spawned the investigation into allogeneic cell therapies, promising significant expansion in the number of treatable patients. The road bumps in developing these therapies have been non-trivial, and the lack of meaningful, large BioPharma support has added to sub-sector headwinds. However, we continue to believe that addressing donor sourcing and managing CMC, regulatory and distribution complexities to generate clinically relevant data in hard-to-treat cancer and rare disease modalities trumps most concerns and are harbingers of the true 'off-the-shelf' promise.

References

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