WHITE PAPER

Decentralized manufacturing: Unlocking CAR-T's potential

An innovative approach to bring therapies closer to patients

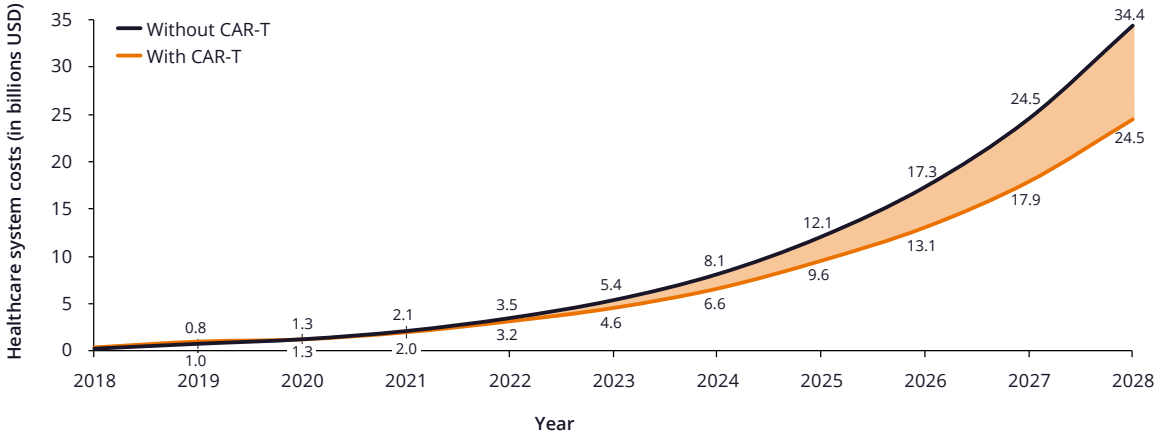
By Romain Bonnot, Pranav Srivastava, Malik Kaman and Trevor Yu

In the six years since autologous chimeric antigen receptor T-cell (CAR-T) therapies became available, many patients who believed they were out of options have benefited from CAR-T's unprecedented outcomes with just one dose. In 2023, the industry saw some of the last decade's most promising hematological therapy outcomes, with readouts like CARVYKTI's CARTITUDE-1 study garnering an overall response rate of 98% and a 27-month progression-free survival rate of 55%.

As CAR-T manufacturers focus on producing more of these life-saving therapies, ZS estimates upfront investments today in CAR-T capacity will pay off in the next five years by reducing healthcare ecosystem expenditures by more than $25 billion. These savings are likely to grow as increasingly durable and effective treatments come to market in new disease areas.

FIGURE 1:

Estimated CAR-T cost savings for the healthcare system



CAR-T experimentation has increased significantly in recent years, with manufacturers starting 91 autologous CAR-T trials in 2023—a 54% increase from the 59 trials started in 2019 and an 11% compound annual growth rate, according to Citeline's Trialtrove. CAR-T clinical trials have largely focused on oncology, spanning both hematology and solid tumors. But in a preview of what could be to come, researchers are exploring how CAR-T therapies could help patients with autoimmune disorders, such as lupus, and help produce more durable response rates while reducing the risk of chronic diseases like graft versus host disease.

The succeeding analysis focuses on autologous cell therapies, which offer the aforementioned benefits but are also prone to unique manufacturing challenges. In this white paper we will explore the pain points of the current centralized manufacturing process and share our perspective on what the future might hold with a decentralized manufacturing model.

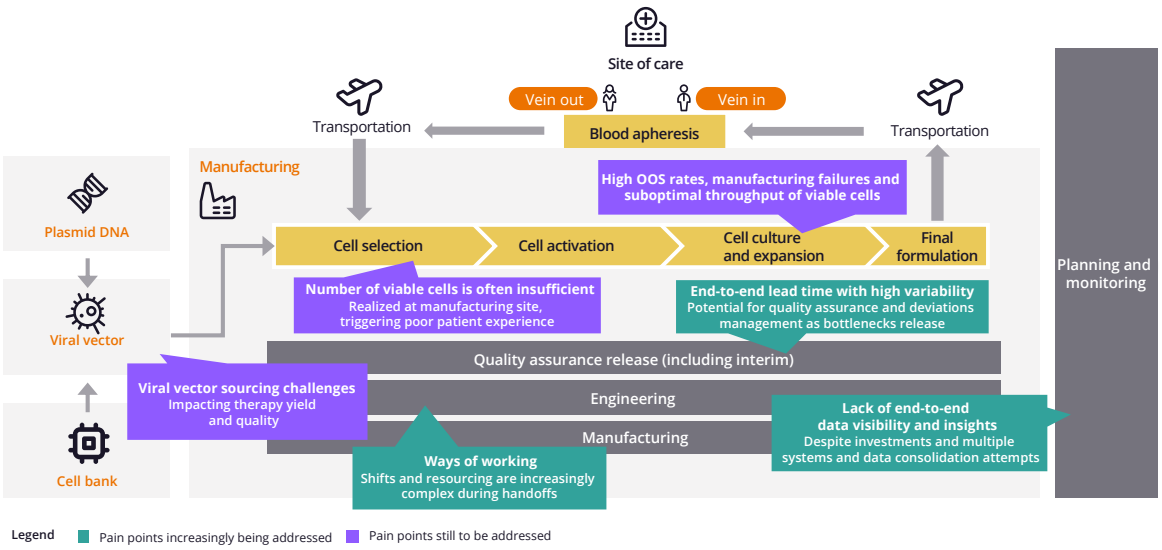
Pain points in autologous CAR-T manufacturing

In addition to go-to-market considerations and payer challenges related to CAR-T pricing, the greatest hurdles to scaling CAR-T effectively and meeting patient demand are vein-to-vein processes and myriad manufacturing considerations. Today, demand for CAR-T exceeds the supply of therapies available. Pain points that have led to this situation include:

- High out-of-specification and manufacturing failure rates
- Complex, country-specific viral vector specifications
- Lengthy and variable lead times that make patient coordination challenging
- Missed therapeutic windows (see Figure 2)

FIGURE 2:

Pain points and bottlenecks hindering vein-to-vein process improvement



These different pain points drive varied levels of impact, which we've summarized in two dimensions. The first is the ability for the manufacturer to control and standardize the process. The second dimension is the economics of the manufacturing process.

We already see manufacturers striving to combat the pain points that have the highest impact on either dimension. They have increasingly focused on reducing end-to-end lead time and variability, improving ways of working through shift optimization, accelerating the escalation path from shop floor to site leadership and exploring investments in digitalization and automation.

Some more technical aspects of the manufacturing process are just now emerging—these include the impact of viral vectors on yield and quality, targeted improvements on out-of-specification rates and total viable cell throughput. These considerations often became apparent later in the process, as companies are improving how they integrate data, deploy systematic in-process controls and in-line and at-line quality controls, and apply advanced analytics and AI.

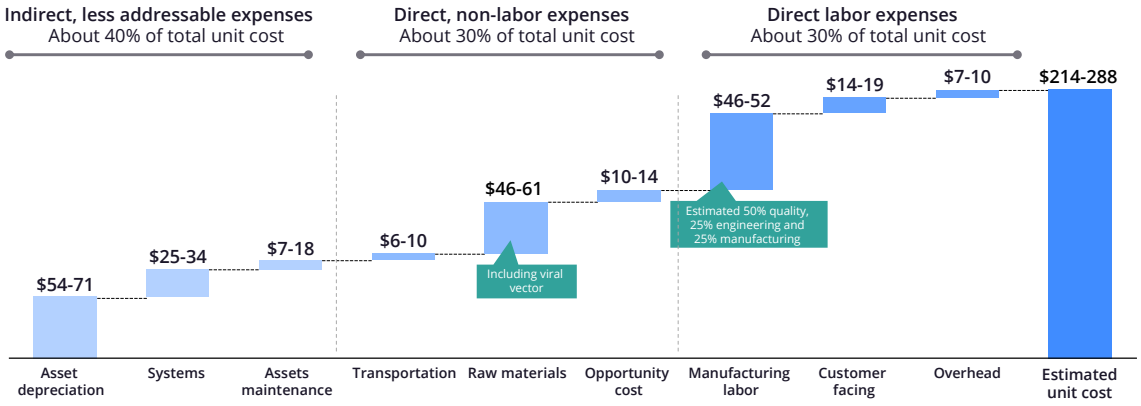
But what about the cost? Our outside-in estimates indicate that the unit cost for an autologous CAR-T therapy could be as high as $250,000-$380,000 per batch. This is because 30%-35% of a therapy's costs, which include asset depreciation, IT, order management systems and asset maintenance are difficult to address. That's not to mention direct non-labor costs, which include $45,000-$70,000 for viral vectors and can comprise 25%-30% of the cost of developing a CAR-T therapy.

As for direct unit costs, they're mainly driven by labor, raw materials and inventory. Opportunity costs, comprised of problems like idle line time and cancellation, are a product of the complex manufacturing process and long lead times. These opportunity costs drive up the expenses associated with developing a CAR-T and play a role in the estimated profit margins of a CAR-T therapy, which are within the 12%-30% range. These margins lag significantly behind other off-the-shelf and traditional modalities.

FIGURE 3:

Autologous CAR-T production: Outside-in unit cost estimates

Estimated unit costs in thousands USD

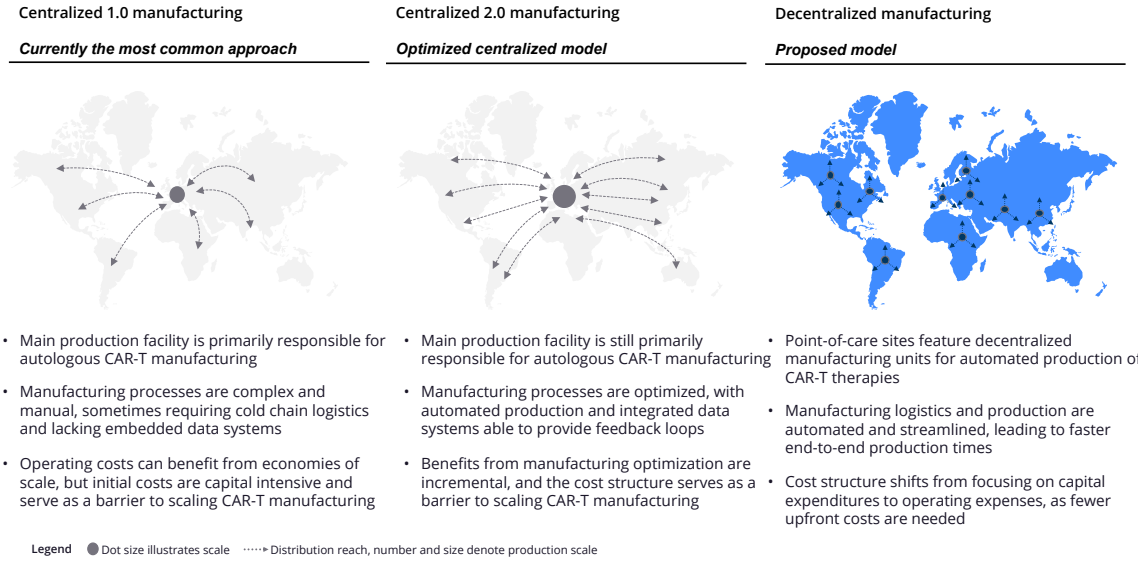


Benefits of decentralized CAR-T manufacturing

We believe decentralized manufacturing is a key approach for addressing CAR-T manufacturing pain points. Borrowed from other industries, decentralized manufacturing is often described as the process of moving production away from a central facility to multiple sites closer to customers.

FIGURE 4:

How decentralized manufacturing can bring production closer to sites of care

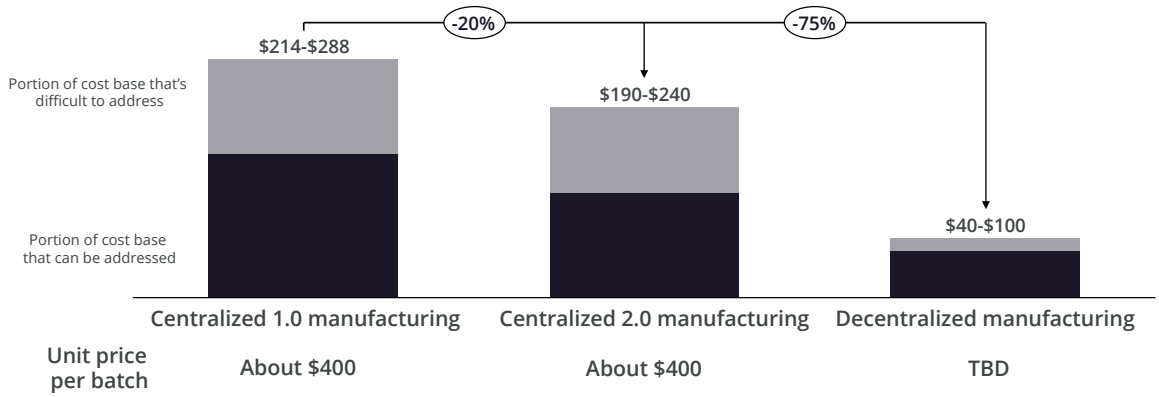


The number of CAR-T manufacturers experimenting with decentralized manufacturing is growing. Many are coupling automated cell therapy platforms—such as Cell Shuttle by Cellares, Lonza's Cocoon, CliniMACS Prodigy by Miltenyi and Ori Biotech's platform—with a decentralized manufacturing process. We believe this approach could be particularly effective, as our directional analysis reveals it presents a synergistic effect that can improve manufacturing economics and ultimately make CAR-T therapies more affordable.

FIGURE 5:

How decentralized manufacturing leads to cost savings

Autologous CAR-T unit cost estimates in thousands USD
Assumes manufacturing of at least 1,000 batches per year



In addition to the economic benefits, coupling decentralized manufacturing with automated closed system manufacturing platforms can improve the patient experience and lead to operational improvements in several areas.

Cryogenic logistics: Manufacturers can use this strategy to simplify cryogenic logistics by streamlining the distance and time from leukapheresis, manufacturing and treatment administration. This decreases the frequency of handoffs between supply chain stakeholders.

This approach can reduce temperature fluctuation risk and out-of-specification rates, bringing more consistently potent autologous CAR-T therapies to patients. It can also decrease the need for temporary storage, as apheresis can be performed when a production slot is ready. Finished goods can be directly transported to the patient, reducing bottleneck constraints from cryogenic storage and improving end-to-end lead time.

Post-leukapheresis: In some cases, there may be insufficient numbers of T-cells extracted from leukapheresis because of the effects of cancer and prior cytotoxic treatment, such as chemotherapy. Decentralized manufacturing with automated cell therapy platforms can offer manufacturers and providers more agility, enabling them to quickly restart the CAR-T production process if needed and limit negative impacts on end-to-end lead time and the patient experience.

Viral vector safety stock and the associated data landscape: Given varying antigen and viral exposure between different geographies, adaptive immune responses may vary across patient populations. The approach we're suggesting offers an increased ability to correlate viral vectors specs to the end-to-end manufacturing process by using a simplified data landscape and applying analytics, including multivariate data analytics. This makes it easier to facilitate contract development and manufacturing organization (CDMO) partnerships that account for specific patient population needs, while also simplifying the local sourcing of raw materials.

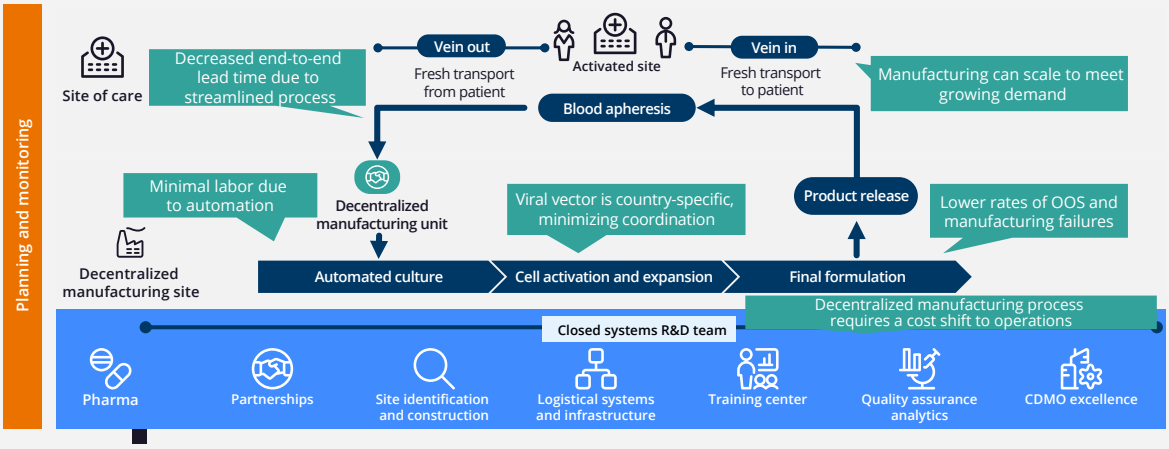
A practical approach to CAR-T decentralized manufacturing

Decentralized manufacturing can both improve the patient experience and increase economic viability, positioning it as an attractive alternative to produce autologous CAR-T therapies. What does this look like in practice, though? With current industry and ecosystem capabilities in mind, we believe decentralized manufacturing will require close coordination between team members at three locations: the sites of care, decentralized manufacturing sites and the manufacturer's headquarters.

FIGURE 6:

A decentralized manufacturing operating model

In this model, manufacturer responsibility shrinks compared to Centralized 1.0 and Centralized 2.0.



To minimize the impact of the transition to decentralized manufacturing, providers can largely maintain processes, such as scheduling and leukapheresis, at their current state during the early stages of the transition. It's crucial for pharma companies to account for a few key levers during the transition.

Operations and processes

Choosing the right production sites, designing effective processes and aptly measuring success are all critical considerations for pharma leaders pursuing a decentralized manufacturing model.

Site identification: To maximize the positive impact on healthcare and ensure sustainable growth, it's vital to develop a well-defined strategy for selecting initial production sites and maintaining sufficient revenue to continue scaling up effectively. It's also important to consider whether sites can be operated through a franchise model, similar to MRI centers, for example, or if they should operate as fully owned stores. The former offers greater scalability but the latter could allow for more CAR-T quality control.

Process design and digital infrastructure: Decentralized manufacturing promises more agility, but this is largely contingent on building a cohesive and digitally powered manufacturing process that can ease logistical burdens for manufacturers and providers, while allowing them to deliver therapies in a timely manner. Close coordination between providers and the manufacturer's commercial team is needed to ensure success and that all parties are up to date during the patient journey. Both groups should be kept abreast about new patients, leukapheresis schedules, infusion dates and more.

Quality assurance analytics: It's been said you cannot improve what you cannot measure. Central to the success of any autologous CAR-T program is the quality inherent in the therapy and the process that produces it. To maintain quality, manufacturers need a strong data analytics backbone that enables the quality assurance team to diagnose and address in real time any issues that cause out of stock (OOS) products and manufacturing failures. The cohesiveness offered by decentralized manufacturing should ease and improve quality assurance processes.

Talent and partnerships

To enable implementation of a decentralized manufacturing model, pharma companies need the right people, capabilities and partnerships in place.

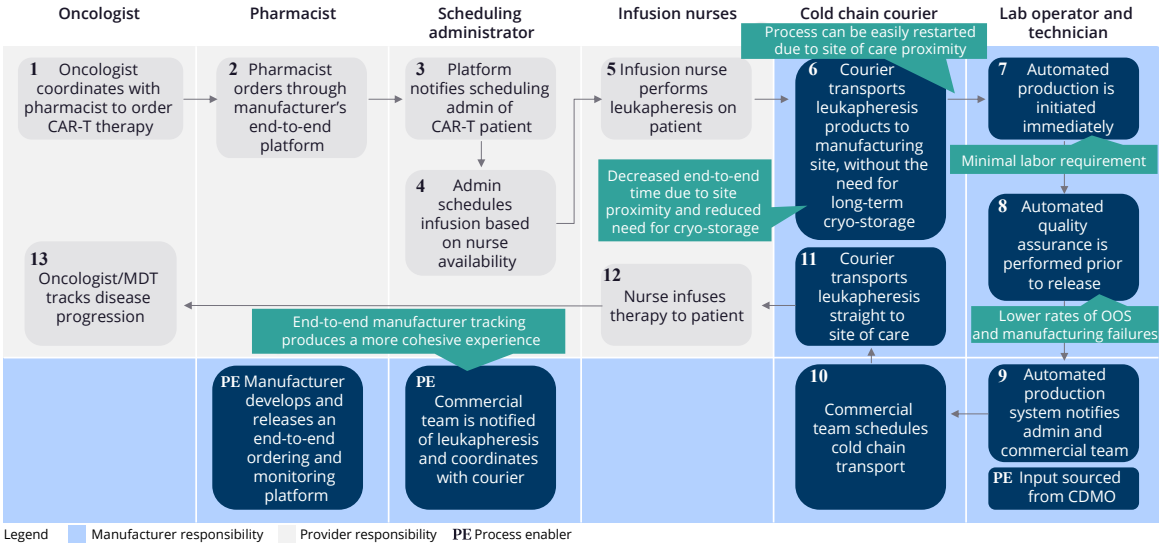
Partnerships: In any major transformation, partnerships play a crucial role in successful implementation. As CAR-T manufacturers transition to a decentralized manufacturing model, they should consider opportunities to partner with automated cell therapy platform manufacturers. As we discussed, together they could lower OOS rates, minimize labor expenditures and increase scalability. Further, establishing strong ties with providers could enable more efficient logistical coordination, allowing manufacturers increased agility to adapt to the changing needs of sites of care.

Training centers: Decentralized manufacturing leads to a wider geographic manufacturing reach, so training will need to be tailored to the needs of each region, country or locality. Team members will need to develop skills ranging from process mastery, troubleshooting, analytics, collaborating with sites of care and other external partners, and understanding quality and regulatory frameworks and their requirements. Pharmaceutical companies will play a leading role in cultivating talent with the right skill sets, and the global shortage of lab professionals will accentuate the complexity of this endeavor and pressure companies to hire, train and retain highly skilled individuals.

CDMO excellence: A particularly pervasive challenge for manufacturers is the constrained supply of raw materials for CAR-T production. These include cell culture media, good manufacturing practice (GMP)-grade cytokines, leukapheresis products, viral vectors and others. These inputs must meet the stringent quality standards for CAR-T therapy, making it critical for manufacturers to establish trusted relationships with CDMOs and other partners that can help ensure sustainability and appropriate purity. Providers can play a role similar to the current manufacturing model, as they can hold a comparable scope of activities along diagnosis, prescription, ordering, scheduling and infusion (see Figure 7).

FIGURE 7:

Ways of working in a decentralized manufacturing model



Considerations for transitioning to decentralized manufacturing

During our conversations with industry leaders, it became clear that decentralized manufacturing might be more suited for development programs than commercial autologous CAR-T manufacturers that currently have a centralized manufacturing model. The incremental benefits that the transformation would bring for in-market assets may not overcome the risks involved:

- Deploying a decentralized model requires scaling geographically across added locations and touchpoints with a broader group of stakeholders, meaning agility and investment are necessary. Additionally, current stakeholders perceive CAR-T therapy quality to be analogous to its production process, making its value sensitive to how it is manufactured.
- Manufacturers with a larger number of existing assets will likely have established apheresis scheduling capabilities, planning and monitoring systems and long-term logistics partnerships in place. They have already invested significant resources to develop and scale their centralized manufacturing operations.

Conversely, for manufacturers with nascent CAR-T programs and robust pipelines, decentralized manufacturing presents significant potential, as these companies will have a blank canvas to develop capabilities well suited to the process. Our estimates suggest facility setup costs to be approximately between $1.5 million-$3 million per decentralized manufacturing site—this assumes three automated cell therapy platforms are producing about 70 CAR-T batches annually—which significantly reduces the need for upfront

investments. This could potentially make the decentralized model more appealing to small to medium-sized players.

Interoperability and the ability to manufacture any autologous CAR-T would add significant value to the business case for decentralized manufacturing, enabling manufacturing flexibility across different CAR-T indications. Small to medium-sized manufacturers could quickly tailor their therapeutic offerings to various types of hospital setups and patient populations.

There are a few key considerations to keep in mind as you plan to set up a decentralized manufacturing model.

Manufacturing distance from sites of care

The manufacturing distance from sites of care underpins decisions around financial viability, operating models and local regulatory strategy. Manufacturers need to assess the business case of being closer to provider facilities by understanding the tradeoffs between microepidemiology, investment requirements and value delivered to the healthcare ecosystem.

While we expect the most prevalent deployment option to be "close to" point of care, the following dimensions are crucial when assessing the distance from point of care:

Space availability: Not all hospitals have the footprint to accommodate a new manufacturing unit. Depending on how closed the platforms are, even a grade B clean room might not be necessary. While we assume a manufacturing unit requires a minimum of 12 square meters, it's worth noting manufacturers can minimize space requirements by using platforms and technologies that enable vertical stacking. Two examples of these are Lonza's Tree technology and Ori Multiplexing.

Internal and external capabilities: The capabilities of a center of care play a key role in co-developing this new way of manufacturing. A manufacturer's ability to identify the right location and space to rent or acquire is also essential. For operations, manual labor will continue to be critical, but the skill sets needed will change. We anticipate a decrease in the pure lab skill set—pipetting and clean room operation, for example—and an increased need for machine operations professionals and on-site technicians. This should lead to reduced headcounts and team members with broader and more holistic skills, ranging from lab operations to troubleshooting.

Location implications: While being closer to centers of care offers obvious partnership benefits, it also brings its own set of complexities on financial models and the exclusive usage of the decentralized manufacturing platforms for one manufacturer.

Platform technology and current limitations

It's also crucial to consider the implications of novel technologies, manufacturing platforms and CAR-T regulations on decentralized manufacturing operations.

Rushing to launch: Because of available GMP-compliant, closed systems that minimize clean room infrastructure investment, many are hopeful the scalability of the decentralized manufacturing model can continue to be improved. Increased automation from these technologies also presents opportunities to standardize production processes, enabling consistency in quality across decentralized sites.

But striving to stabilize: The nascency of "lab-in-a-box" technology means some platforms are currently experiencing limitations as they work to improve the overall manufacturing experience. Because most processes still require some form of manual work in the longer term, it may be beneficial to explore automated processes and leveraging AI and ML to adapt production to patient- and therapy-specific needs.

Regulatory oversight: Of course, regulatory oversight is an important consideration for CAR-T manufacturers, and we believe a regulatory evolution will be needed to support decentralized autologous CAR-T manufacturing. There is a pervasive notion from healthcare stakeholders—especially regulators—that "the process is the product, and the product is the process." This makes it especially important to understand regulator perceptions of decentralized manufacturing and its challenges. Gaining insights into whether this new CAR-T production process should be categorized as a technology transfer or a new product launch will also be vital. Once manufacturers have a better handle on this information, they will need to refine a market access strategy to navigate the regulatory environment and realize its potential impact on the CAR-T ecosystem.

Decentralized manufacturing: The time to act is now

While the novelty of the decentralized manufacturing process presents a complex set of considerations, it also brings forth the potential for much-needed innovation in an industry stymied by supply chain constraints. By pivoting to the decentralized manufacturing model, companies can futureproof themselves for the inevitable increased demand for CAR-T therapies, while also bringing benefits to patients, providers and payers. Manufacturers that capitalize on this opportunity in the near-term will be able to experience the advantages of being early adopters, including the opportunity to build critical relationships that enable a robust CAR-T manufacturing process.

About the authors

Romain Bonnot is a senior partner and the EU lead for ZS's strategy and transformation practice. Romain enables life sciences organizations—including pharma, medtech, private equity and investment companies and health insurance—on strategic topics across the value chain, with a focus on large scale operating model transformations, supply chain and manufacturing strategy, business development and licensing and mergers and acquisitions. He rejoined ZS from Novartis, where he was vice president and global head of strategy for oncology. Romain is a trained pharmacist, earned a MBA from ESCP Business School and is an alumnus of INSEAD executive education programs.

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Trevor Yu is a member of ZS's strategy and transformation practice in the EU. His experience spans operating model design, digital transformation and product strategy, with a focus on oncology. Trevor joined ZS from the pharmaceutical industry, where he was responsible for a portfolio of oncology products. He holds a master's in management degree from INSEAD and a B.S. in molecular, cellular and developmental biology from the University of California, Los Angeles.

About ZS

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