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A simulation-based comparison of centralized and point-of-care supply chain strategies for autologous cell therapy

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ABSTRACT

Background aims: The selection between centralized and point-of-care (POC) manufacturing supply-chain network design is a crucial consideration in the autologous cell therapy (AuCT) industry, as each approach offers its advantages and disadvantages.
Methods: This study uses a simulation-based approach to compare and examine the two strategies using the supply chain for chimeric antigen receptor T-cell therapy manufacturing as an exemplar. When does it make sense to use one manufacturing strategy over another? Currently, major manufacturers in the AuCT industry use centralized supply-chain strategies predominantly in practice. The simulation results explain the reasons for this choice. To enhance the competitiveness of the POC strategy, two operation rules are proposed and tested with the simulation. The study uses key performance indicators such as cost, fulfillment time, service level, and resource utilization to provide generic guidelines based on the findings.
Results: The results have revealed that (i) the centralized supply-chain strategy has a significant advantage at current demand levels of a few thousand products per year; (ii) "optimal capacity" exists for the POC strategy that minimizes the cost of goods and (iii) allowing part-time labor and order transshipment can significantly increase the competitiveness of the POC strategy.
Conclusions: This study may be useful in helping commercial manufacturers make informed decisions about their manufacturing approach to enhance their competitiveness in the market and to ensure a high level of patient benefit.

Introduction

Autologous cell therapy (AuCT) is an emerging field of medicine that offers significant promise for the treatment of a variety of diseases [1,2]. However, with the growing demand for AuCT products, manufacturers in this new field of medicine must find effective and cost-efficient manufacturing and supply-chain methods to remain competitive and to be able to provide these therapies to as many patients as could possibly benefit. A crucial consideration in the AuCT industry is the selection between centralized and decentralized manufacturing approaches, with each offering unique advantages and disadvantages [3].

Centralized manufacturing offers economies of scale and efficient resource use [4], but it may result in longer wait times for patients and logistical challenges in product distribution. In contrast, decentralized or point-of-care (POC) manufacturing allows for reduction in the transport time of cellular raw material and the final product, but it has increased operational costs and complexity in the supply chain. Therefore, there is added effort needed to ensure a level of process consistency across multiple facilities and quality control/quality assurance at low-volume manufacturing sites. The decision of which approach to use is complex and depends on various factors, including the type of cells being manufactured, the size of the target market and demand distribution [5,6].

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To make an informed decision, it is necessary to consider each approach's benefits and drawbacks. There are also configurations using a mixed strategy between these two extreme cases, often referred to as "regional hub" approaches. All these options of supply chain configurations can form a spectrum characterized by the degree of centralization, which is a hard-to-determine parameter depending on various factors, including the type of cells being manufactured, the size of the target market and the demand distribution. In addition, the unique features of AuCT products, such as high personalization, complexity, regulatory oversight, high cost, medical supervision, cold-chain management and high uncertainty in quality control, reduce the sufficiency of conventional supply-chain design tools. Choosing the best degree of centralization has become one of the most common challenges facing existing and potential manufacturers of AuCT products, according to recent studies [7,8].

This article presents a simulation-based study that examines and compares the centralized and decentralized approaches in AuCT manufacturing using a validated agent-based simulation tool. Specifically, the study uses the supply chain of chimeric antigen receptor (CAR) T-cell therapy as an exemplar to provide insights into the trade-offs involved in the decision-making process and offers generic guidelines based on the findings. The study focuses on key performance indicators such as cost, fulfillment time, service level and resource utilization to reduce the complexity of the problem. Other important considerations, such as quality risks, regulation policy, manufacturing space limitations at the health care center, repurposing of personnel at POC sites, one versus many suppliers, tax and other factors, are acknowledged but not included in the scope of the present comparison study.

Literature Review

There is existing research on comparing centralized and decentralized supply chain models for AuCT products. The study conducted by Lam *et al.* [9] is one such research effort that evaluated the performance of these two supply chain models in the United Kingdom using discrete event simulation and indicators such as cost per treatment, treatment turnaround time and resource utilization. The study found that although the decentralized model had a shorter turnaround time per treatment, this advantage was insignificant in the United Kingdom due to its compact geography and established transportation networks. In contrast, the centralized supply chain model was more cost-effective and efficient due to economies of scale. However, at high demand levels, cooperating individual facilities in a decentralized system were able to spread facility costs across more treatments and better utilize resources, resulting in a more comparable cost per treatment. Based on these findings, the authors concluded that the decentralized model does not offer significant advantages in the United Kingdom over centralized manufacturing, given the country's smaller demand and geographic setting. However, the study did not consider supplier base or labor shortage uncertainties, capacity constraints or quality risks associated with the two supply chain models.

In another study, Wang *et al.* [10] conducted a multi-objective optimization analysis to determine the optimal location of CAR T-cell therapy production facilities in the global supply chain. The study found that the optimized supply chain model, which has six global manufacturing centers, could lead to greater net present value and short average response time. However, the authors noted that further research is needed to examine the impact of capacity constraints and supplier reliability on the performance of the supply chain models.

Karakostas *et al.* [11] evaluated a new patient-centric, decentralized supply chain model for CAR T-cell therapies proposed by stochastic optimization using a general variable neighborhood search algorithm. Their model used mobile medical units to deliver therapies and transport specialized medical staff to the local treatment facilities. The study suggested that opening more manufacturing centers may lead to a significant routing cost reduction due to the opportunity for selecting more efficient routes.

Overall, although the existing literature provides some insights into the advantages and disadvantages of centralized and decentralized supply chain models for CAR T-cell therapies, further research is needed to address the gaps and limitations of previous studies. In this study, we use the agent-based simulation framework proposed by Wang *et al.* [12] to model centralized and decentralized CAR T-cell therapy supply chains in the United States. The simulation framework incorporates various key features, including a multiscale structure, multiple key performance indicators (KPIs), stochasticity where applicable and a highly scalable framework. The multiscale structure includes a micro-scale model that reflects the activities within health care centers and manufacturing facilities and a macro-scale model that simulates the AuCT supply chain network and associated activities, including allocating health care centers and manufacturing facilities and transportation activities. The multiple KPIs can be categorized into time-related, efficiency-related and cost-related indicators. The contribution of this work can be summarized as follows:

- Conducted a comparative analysis between centralized and decentralized POC supply chains for CAR T-cell therapy within the United States, accounting for increased demand and diverse geographical configurations.
- Contributed insights into the determination of optimal capacity for individual POC facilities, enabling quantitative cost analysis and resource allocation during times of fluctuating demand.
- Investigated the advantages inherent in demand or production capacity sharing within a decentralized network model, substantiating the feasibility of cost-minimization approaches.

Methodology

Based on existing research, it can be concluded that centralized manufacturing layouts offer clear advantages over POC manufacturing layouts in terms of cost and quality control. Furthermore, centralized manufacturing layouts can leverage economies of scale more effectively as demand increases. However, centralized manufacturing layouts require a substantial initial investment and robust global resource scheduling capabilities, creating a significant barrier to entry for new and small manufacturing enterprises. In contrast, the POC model may be more suitable for start-ups and small businesses that begin at a local level and gradually increase investment as they grow. In the emerging cell therapy industry, if both centralized and POC manufacturing strategies are viable under specific circumstances, manufacturers of different sizes can adopt supply-chain strategies that align with their capabilities, fostering a more robust industrial ecosystem. Nevertheless, the reality is that centralized manufacturing holds significant advantages in this industry, making it challenging for start-ups and small-to-medium-sized enterprises to thrive.

In this study, we explore whether it is possible to propose some strategies to enhance the cost-effectiveness of the POC model based on the characteristics of the cell therapy industry so that, under certain conditions, the POC model can compete with centralized manufacturing costwise. We will verify the following two potential strategies, including:

S1. Allowing POC to use part-time labor
S2. Allowing orders to be transferred between different POC nodes

Design of computer experiments

The computational experiments will be performed on a previously developed supply chain simulation platform [12]. The overall demand level will be varied from 500/year to 20000/year. Order will be randomly generated at one of the 20 clinics distributed in the contiguous United States. The list of these certified clinics and their locations is included in the supplementary Materials. For each demand level, five supply chain scenarios will be evaluated:

- Scenario C: Centralized supply chain

All orders will be processed in one manufacturing facility. The location of the centralized facility was selected by using Kite's manufacturing facility in Southern California.

- Scenario R: Regional hubs supply chain

All orders will be processed in two manufacturing facilities, one on each coast of the contiguous United States. The locations of the regional hubs were selected by using Kite's manufacturing facility in Southern California and Maryland.

- Scenario P: POC supply chain

The orders will be processed in the POC nodes associated with the 20 clinics. The locations are assumed to be the same as the clinics.

- Scenario P+S1: A variant of the POC supply chain with part-time labor allowed

The configuration is the same as Scenario P except that the salaries of operators are paid based on the actual hours spent on the production line instead of a fixed yearly rate.

- Scenario P+S2: A variant of the POC supply chain with order transfer allowed

The configuration is the same as Scenario P+S1, except that any POC node can transfer new orders to other POC nodes with available manufacturing capacity if all local capacity is occupied.

The performance metrics include cost of goods, order fulfillment time, and resource utilization. Other assumptions used in the computational experiments include those discussed in the sections to follow.

Process-related assumptions

If both cell collection and therapy administration take place within the same health care facility for a patient, a representative workflow is depicted in Figure 1. A stochastic process, such as the Poisson process, is used to characterize the arrival of patients. Upon a patient's arrival, the health care center establishes a treatment schedule and generates a therapeutic order for a manufacturing facility based on predefined rules. For scenarios "C," "R," "P" and "P+S1," the nearest facility is selected, whereas in the "P+S2" scenario, priority is given to the facility with the highest-available capacity. After the manufacturing process, the therapy is shipped back to the health care center, where it awaits administration. Once the cell therapy product has been released, the patient is scheduled to undergo a preconditioning chemotherapy regimen several days prior to receiving the cell therapy.

The therapeutic manufacturing workflow is illustrated in Figure 1. The process begins with the receipt and acceptance of a patient's biological specimen at a manufacturing facility. Upon acceptance, the specimen is placed in a queue, awaiting the availability of bioreactors, personnel and consumable resources. Once the necessary resources are allocated, the specimen undergoes processing, which includes enrichment and activation, followed by transduction using a lentiviral vector. The genetically modified T cells are then expanded, harvested, formulated and cryopreserved in preparation for transportation. To ensure the safety and efficacy of the therapy, quality control tests are conducted before the treatment is shipped back to the treating center. Once the treatment successfully passes the quality control tests, it is released for shipment. It is important to note that cryopreservation is assumed required for all scenarios, even for the POC supply chain where transportation is unnecessary.

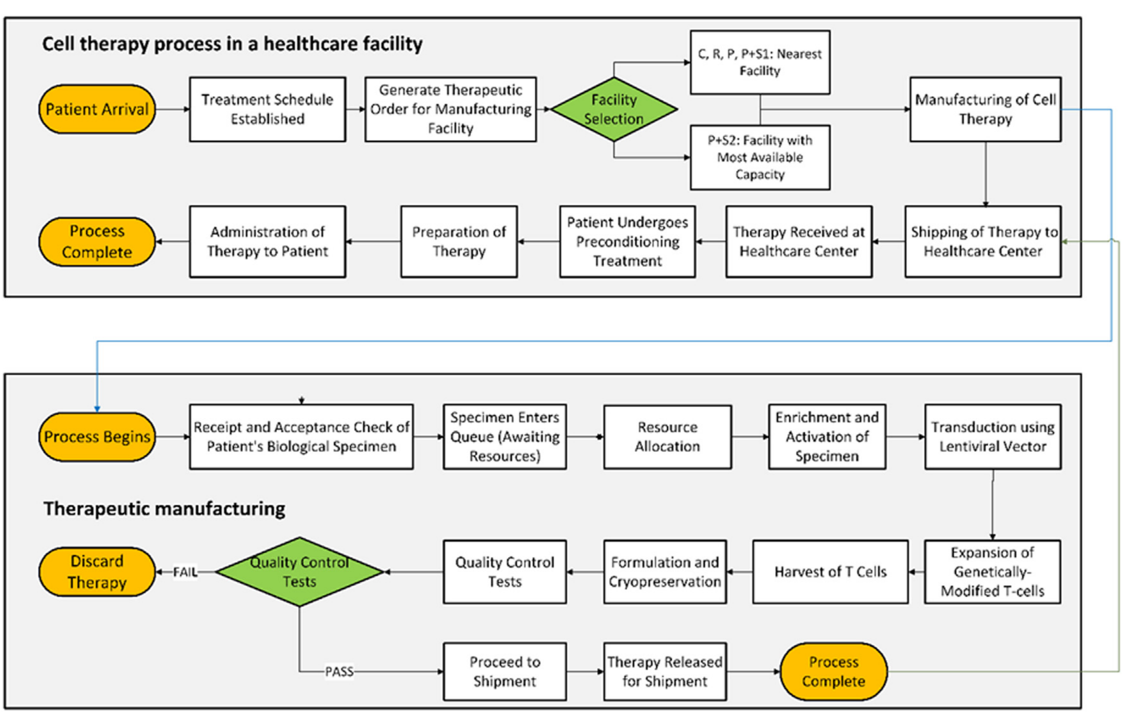

Figure 1. Typical process flow of CAR-T therapy in health care facilities and manufacturing sites. (Color version of figure is available online.)

Distribution-related assumptions

Transportation of patient specimens and therapy products is considered in the centralized supply chain (Scenario C), regional hubs supply chain (Scenario R) and the POC supply chain with order transfer (Scenario P+S2). In these scenarios, it is assumed that therapy will be shipped promptly upon completion of production. Ground transportation is used for distances up to 300 miles, whereas air transportation is employed for distances beyond this threshold. The transportation times for Scenarios C and R were obtained from Google Maps and can be found in supplementary Table 1. In addition, it is assumed that there are preparation periods before and after transportation activities, with a total preparation time of two hours for ground transportation and four hours for air transportation. In the case studies, the term "turnaround time" refers to the duration from the initiation of shipping a patient's specimen to the receipt of the final therapy product.

Cost-related assumptions

Annual personnel costs. In this study, we consider the costs associated with manufacturing personnel (C^{pers}), which include production staff, quality assurance (QA) specialists, quality control (QC) analysts and qualified persons (QP). We employ two methods to calculate the annual personnel costs for each manufacturing facility.

The first method, based on an annual salary, calculates the annual personnel costs by multiplying the number of personnel for each category ($n^{pers}_{QA,y}$, $n_{QC,}\ y^{pers}$, $n_{QP,}\ y^{pers}$) by their respective annual salaries ($c_{QA,}\ y^{pers}$, $c_{QC,}\ y^{pers}$, $c_{QP,}\ y^{pers}$), as expressed in Equation 1.

$$C^{pers} = n^{pers}_{QA,y} * c^{pers}_{QA,\ y} + n^{pers}_{QC,\ y} * c^{pers}_{QC,\ y} + n^{pers}_{QP,\ y} * c^{pers}_{QP,\ y} \tag{1}$$

The second method, using an hourly wage, computes the annual personnel costs by multiplying the total number of working hours for each personnel category ($n^{pers}_{QA,h}$, $n_{QC,}\ h^{pers}$, $n_{QP,}\ h^{pers}$) by their corresponding hourly pay rates ($c_{QA,}\ h^{pers}$, $c_{QC,}\ h^{pers}$, $c_{QP,}\ h^{pers}$), as denoted by Equation 2.

$$C^{pers} = n^{pers}_{QA,h} * c^{pers}_{QA,\ h} + n^{pers}_{QC,\ h} * c^{pers}_{QC,\ h} + n^{pers}_{QP,\ h} * c^{pers}_{QP,\ h} \tag{2}$$

Annual equipment costs. In this study, we examine the expenses related to manufacturing equipment. The annual equipment costs (C^{eqp}) are computed by incorporating the quantity of each equipment type (n^{eqp}_i), its respective purchase cost (c^{eqp}_i) and a depreciation factor (γ^{eqp}), as expressed in Equation 3. The annual equipment costs do not include the costs of maintenance contracts for major equipment. The number of each equipment is determined by using a target service level under different demand levels. A comprehensive list of equipment and corresponding costs is available in supplementary Table 2.

$$\mathrm{C}^{\mathrm{eqp}} = \gamma^{\mathrm{eqp}} * \sum_{\mathrm{i}} \mathrm{n}^{\mathrm{eqp}}_{\mathrm{i}} * \mathrm{c}^{\mathrm{eqp}}_{\mathrm{i}} \tag{3}$$

Annual facility costs. The annual facility costs (C^f), are comprised of the capital and utility expenditures (C^f_{cap}, C^f_{util}), and a re-validation fee ($C^f_{re-valid}$) associated with manufacturing facilities. The facility capital costs (C^f_{cap}) are determined by considering the total floor space occupied by the equipment (A^f), the construction cost per unit area (c^f_{cap}) and the depreciation factor (γ^f), as illustrated in Equation 4.

$$C^f_{cap} = \gamma^f * A^f * c^f_{cap} \tag{4}$$

The facility utility costs (C^f_{util}) are computed by considering the total floor space occupied by the equipment (A^f) and the utility cost per unit area (c^f_{util}), as expressed in Equation 5.

$$C^f_{util} = A^f * c^f_{util} \tag{5}$$

The total floor space (A^f) is derived from the number of individual units (n^{eqp}_i) and their respective occupied areas (a^{eqp}_i), as expressed in Equation 6.

$$A^f = \kappa * \sum_i n^{eqp}_i * a^{eqp}_i \tag{6}$$

Note that a three-foot allowance is allocated for the width and depth of each piece of equipment to accommodate exhaust requirements. Furthermore, additional working space for operation and maintenance and a Good Manufacturing Practice working space multiplier (κ) are considered for the indirect working area requirements. The capital and utility costs per unit area, along with a list of equipment and corresponding dimensions considered in this study, are provided in supplementary Table 2.

Annual consumable costs. The annual consumable costs (C^{cs}) are calculated based on the yearly material consumption throughout the manufacturing process, encompassing stages such as quality assessment, cell isolation, activation, transduction, expansion and cryopreservation. A comprehensive breakdown of the costs associated with these manufacturing steps can be found in supplementary Table 3.

Annual transportation cost. The annual transportation cost is the summation of the total transportation costs (C^{trans}) for all therapy. The total transportation costs (C^{trans}) comprise the expenses incurred by the vehicle (c^{trans}) and the delivery personnel (c^{trans}_{pers}), as expressed in Equation 7.

$$C^{trans} = c^{trans} + c^{trans}_{pers} \tag{7}$$

The vehicle costs (c^{trans}) vary between air and ground transportation modes. For air transportation, c^{trans} is determined by the price of a one-way flight ticket, with pricing data obtained from Google Maps. In contrast, for ground transportation, c^{trans} is calculated by multiplying the travel distance by the delivery cost per mile. A comprehensive list of flight ticket prices, travel distances, and delivery costs per mile is provided in supplementary Table 1.

The delivery personnel costs (c^{trans}_{pers}) are derived from the delivery time and the personnel's hourly salary rate. The transportation times and personnel's hourly salary rates can also be found in supplementary Tables 1 and 2. It is essential to note that the transportation costs (C^{trans}) for each therapy are computed for shipping a patient's specimen from the health care center to the manufacturing facility and the return of the final product back to the health care center.

Cost of goods. The cost of goods (*COGS*) is the total annual cost (C^{annual}) divided by the total number of therapies ($N^{therapy}$) delivered in the year, as expressed in Equation 8.

$$COGS = \frac{C^{annual}}{N^{therapy}} = \frac{C^{pers} + C^{eqp} + C^f + C^{cs} + C^{trans}}{N^{therapy}} \tag{8}$$

Data-collection methods

The annual demand for the commercial CAR-T cell therapy, Yescarta, is estimated to be approximately 3600, as reported in a 2022 Q4 public disclosure [13]. Yescarta has recently demonstrated a significant improvement in survival rates among patients with relapsed/refractory large B-cell lymphoma [14]. In the United States, more than 18 000 individuals are diagnosed with LBCL annually, with approximately 30−40% of these patients requiring second-line treatment.

Yescarta is but one of six approved CAR-T cell therapies and many more currently being developed. By 2025, the U.S. Food and Drug Administration anticipates approving 10−20 cell and gene therapies annually [15]. To accommodate the varying demand scenarios for CAR-T cell as an exemplar and model for other similar therapies at different stages of commercialization, we conducted an in-depth investigation. The demand arrival process in this case study employs a Poisson process with six rates: 200, 500, 1000, 5000, 10 000 and 20 000 patients per year.

The number of equipment and personnel for the manufacturing facilities in all supply chain configurations, e.g., three supply chain models under three annual demand levels, is determined using the simulation optimization module with the constraint of service level greater than or equals to 95% for all process stages.

In Scenario P+S2, we investigate the potential benefit of demand sharing in the POC supply chain. A heuristic rule is implemented in the proposed supply chain simulation to facilitate demand sharing across the POC facilities. The logic of the heuristic rule is detailed in Algorithm 1. The objective of the demand-sharing algorithm is to determine the optimal manufacturing facility for an AuCMP order, considering the availability of bioreactors and qualified personnel.

Initially, the algorithm examines the availability of manufacturing capacity, including bioreactors and qualified personnel, at the local facility. Without available capacity, it sorts the manufacturing facilities according to their proximity to the current POC location. Subsequently, the algorithm assesses the capacity availability at each facility, from near to distant, and selects the one offering the maximum available capacity. It is important to note that if there are multiple facilities with the same maximum available capacity, the algorithm will select the nearest facility. In cases where no other facility possesses available capacity, the algorithm expands additional manufacturing capacity to the local facility and proceeds to process the order at that location.

The simulation model is developed using the Java API and AnyLogic library 8.7.7 on a desktop PC with 2.40 GHz, Intel(R) Core (TM) i7-9700K CPU, 16.0 GB RAM, and Microsoft Windows 10 operating system (64-bit). In the Results section, the simulation outcomes presented are derived from the mean values of 10 independent replications for each respective scenario, with each replication being a simulation run with a 1-year time horizon.

Results

Scale-up analysis

The demand for CAR T-cell therapies exceeds the limited availability of certified infusion sites and manufacturing slots annually. As the technologies and systems continue to mature in the field, it is anticipated that the cost of CAR T-cell therapies will decrease, while demand remains high and is likely to increase due to approvals in additional indications and a rising incidence of applicable disease indications. This growing demand can be partially addressed by improving efficiencies in production through the streamlining of the process, such as the integration of additional automation and the shortening of the process [16]. Scaling up production to meet this growing demand will require expanded manufacturing facilities with greater production capacities, whether through a centralized manufacturing scenario or a regional hubs scenario. However, in the case of a POC scenario, the increased demand may necessitate an expansion of certified treatment infusion centers and POC sites instead.

Figure 2 shows Scenarios C (Centralized), R (Regional) and P (POC) simulation results in various demand levels for the entire network. Note that for Scenario P, we assume that the capacity of POC is fixed and the number of POC sites will increase proportionally with the annual demand, as summarized in Table 1.

The findings suggest that the POC model may not experience the same level of benefits from economies of scale as the centralized and regional hub models, potentially due to the utilization of resources. Specifically, the random nature of demand in the time domain may require each manufacturing facility in the POC model to maintain a certain amount of redundancy in resources to cope with demand fluctuations. This redundancy can result in greater costs and reduced efficiency in contrast to the centralized and regional hubs models, which can consolidate resources and optimize their utilization to take advantage of economies of scale. This is evidenced by the lower

Algorithm 1
Heuristic rule for demand sharing

```
Inputs:
    POC location of the current AuCMP order
Outputs:
    Selected manufacturing facility for the AuCMP order
Let the number of bioreactors be one at all manufacturing facilities
Let the selected facility be at the POC location of the current AuCMP order
Let shareDemand = False
Check the number of available bioreactors at the local facility: localBio
if localBio > 0 then
    Process the order at the local facility
else
    Let maxCapacity = localBio
    Sort the list of manufacturing facilities by the distance to the current POC location,
from near to far
    for facility in the list of facilities do
        Check the number of available bioreactors: tranBio
        if tranBio > maxCapacity then
            maxCapacity = tranBio
            Change the selected facility to this facility
            shareDemand = True
        end if
    end for
    if shareDemand = False then
        Add one bioreactor to the local facility
        Process the order at the local facility
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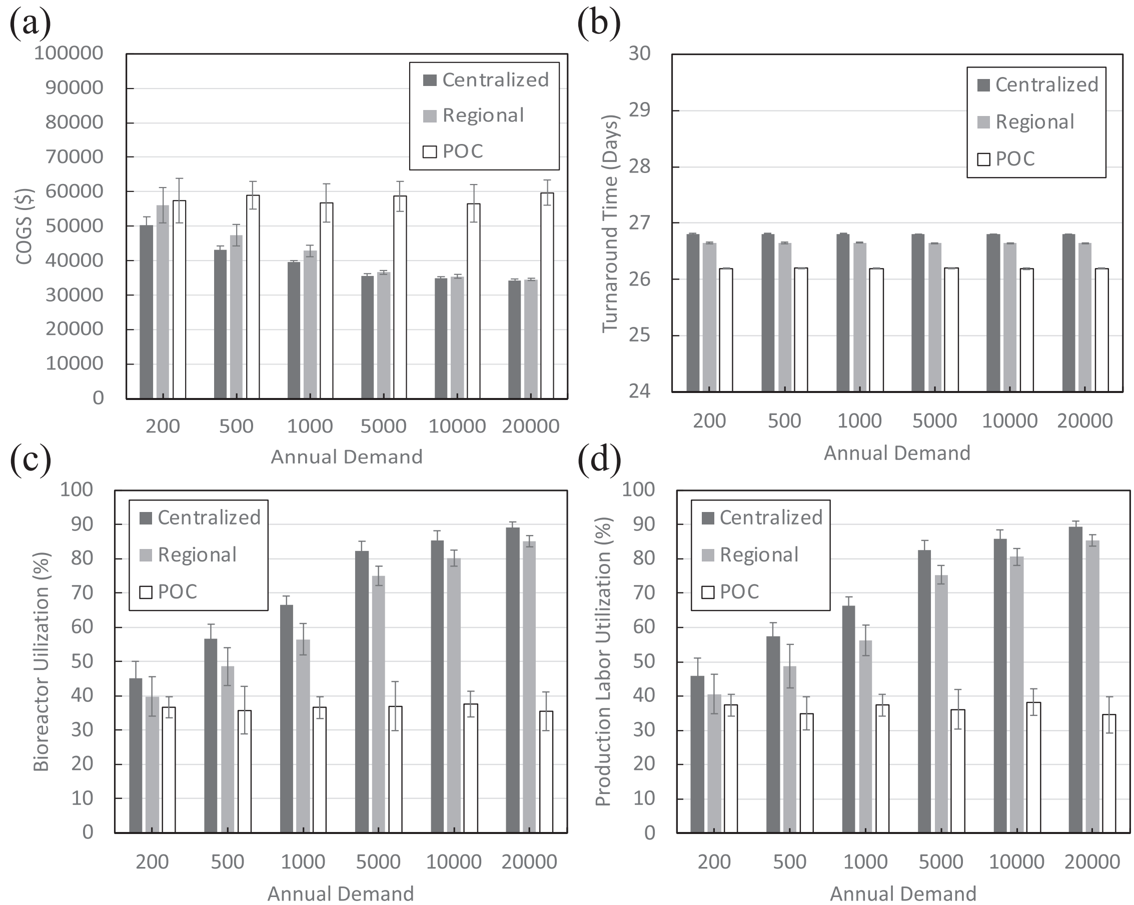

Figure 2. Comparison of centralized, regional hubs and POC in (a) COGS; (b) turnaround time; (c) bioreactor utilization rate and (d) production labor utilization rate. COGS, cost of goods sold.

overall resource utilization for the POC model, as illustrated in Figure 2C.

We conducted some follow-up simulations to investigate further the impact of maximum capacity of each POC site on the scale-up efficiency. In these simulations, we assume there are 20 POC sites and allow the POC sites to grow in capacity as the overall demand grows. The capacity of each POC site under different demand levels for the entire network is summarized in Table 2. We simulated different POC configurations with different maximum capacities at each demand level. The results are illustrated in Figure 3.

Based on the results presented in Figure 3, it appears that extrapolating to extremely high annual demand there may be a critical manufacturing capacity for POC sites above which the overall scale-up efficiency of the POC scenario could potentially surpass the centralized scenario. It should be noted, however, that the critical capacity may vary depending on the specific product being manufactured and the associated cost configurations. For the cost configuration used in this case study, the critical capacity for POC sites was approximately 200 patients per POC site per year. It is important to recognize that this capacity may not be generalizable to all contexts and that additional research is needed to identify critical capacities for other product types and cost configurations.

Another argument is that increasing the capacity of a single POC facility cannot be considered a "pure" POC strategy. As the number of certified clinics increases, the number of POCs required does not necessarily increase proportionally due to the increase in capacity of a single facility. As a result, the final supply chain network may consist of each POC site being responsible for the orders of multiple clinics, effectively functioning as a small regional hub. Consequently, allowing POC capacity to increase may ultimately lead to forming a mixed-strategy supply chain network. This network would consist of a combination of POC and regional hub strategies, with POC sites functioning as small regional hubs to support the overall supply chain.

Overall, these findings suggest that the optimal manufacturing strategy may depend on the manufactured product and associated cost configurations. Manufacturers should therefore carefully

Table 1
Number and capacity of each site for Figure 2.

	C		R		P (100 patients/year)	
Annua demand	No. of sites	Capacity	No. of sites	Capacity	No. of sites	Capacity
200	1	200	2	100	2	100
500	1	500	2	250	5	100
1000	1	1000	2	500	10	100
5000	1	5000	2	2500	50	100
10 000	1	10000	2	5000	100	100
20 000	1	20 000	2	10 000	200	100

Table 2
Number and capacity of each site for Figure 3.

	C		R		P	
Annual demand	No. of sites	Capacity	No. of sites	Capacity	No. of sites	Capacity
200	1	200	2	100	20	10
500	1	500	2	250	20	25
1000	1	1000	2	500	20	50
5000	1	5000	2	2500	20	250
10 000	1	10 000	2	5000	20	500
20 000	1	20 000	2	10 000	20	1000

evaluate the trade-offs between different manufacturing models and capacities to determine the most efficient and cost-effective manufacturing strategy for their context. In addition, future research could explore the impact of different manufacturing strategies on supply chain performance metrics, such as delivery times, costs, and environmental sustainability, to help inform decision-making in this area.

The impact of additional POC rules

The unique features of cell therapy manufacturing create opportunities to implement specialized rules for the POC strategy, potentially increasing its competitiveness. One such feature is that POC sites are typically attached to clinics. Moreover, the skill set required for cell therapy manufacturing and quality control is similar to that of stem cell transplant laboratory technicians. As a result, it may be reasonable to incorporate some cell therapy manufacturing and quality control cross training for some employees of the stem cell transplant laboratory.

This approach would allow employees to allocate their workload between cell therapy manufacturing and stem cell transplant laboratory. It could also help to reduce the waste of labor resources due to demand fluctuations, which are common in cell therapy manufacturing. It should be considered, however, that demand fluctuations in these cases may not be complementary. To implement a complementary scenario in the simulation, the labor cost is calculated by actual person-hours spent on cell therapy manufacturing/quality control instead of fixed salaries for operators (Scenario P+S1).

Another potential rule is to allow order sharing among POC nodes to address the demand uncertainty in the POC strategy. In the original POC setup, each site manages its own local demand fluctuations, which can result in high levels of redundancy in resources. However, if shipping and chain of custody qualification, regulatory, and legal hurdles are cleared POC nodes could transfer new orders to other nodes with available capacities when their own capacities are occupied, they become potential capacity at times of POC site waxing demand. Meeting these requirements typically demands substantial collaborative efforts among multiple stakeholders and should not be underestimated.

This approach would enable cooperating POC sites to deal with the overall demand fluctuation, potentially reducing redundancy in the network. Although this may result in occasional increases in

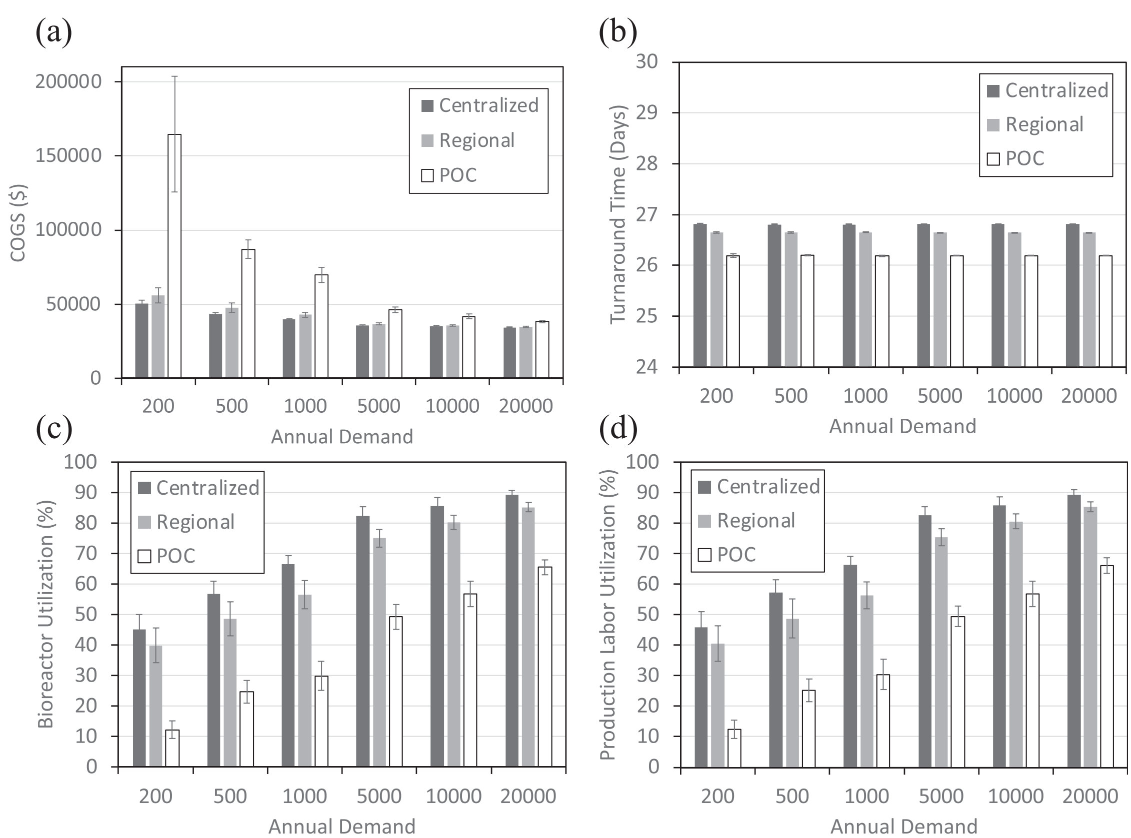

Figure 3. Comparison of centralized, regional hubs and POC with different capacities in (a) COGS; (b) turnaround time; (c) bioreactor utilization rate and (d) production labor utilization rate. COGS, cost of goods sold.

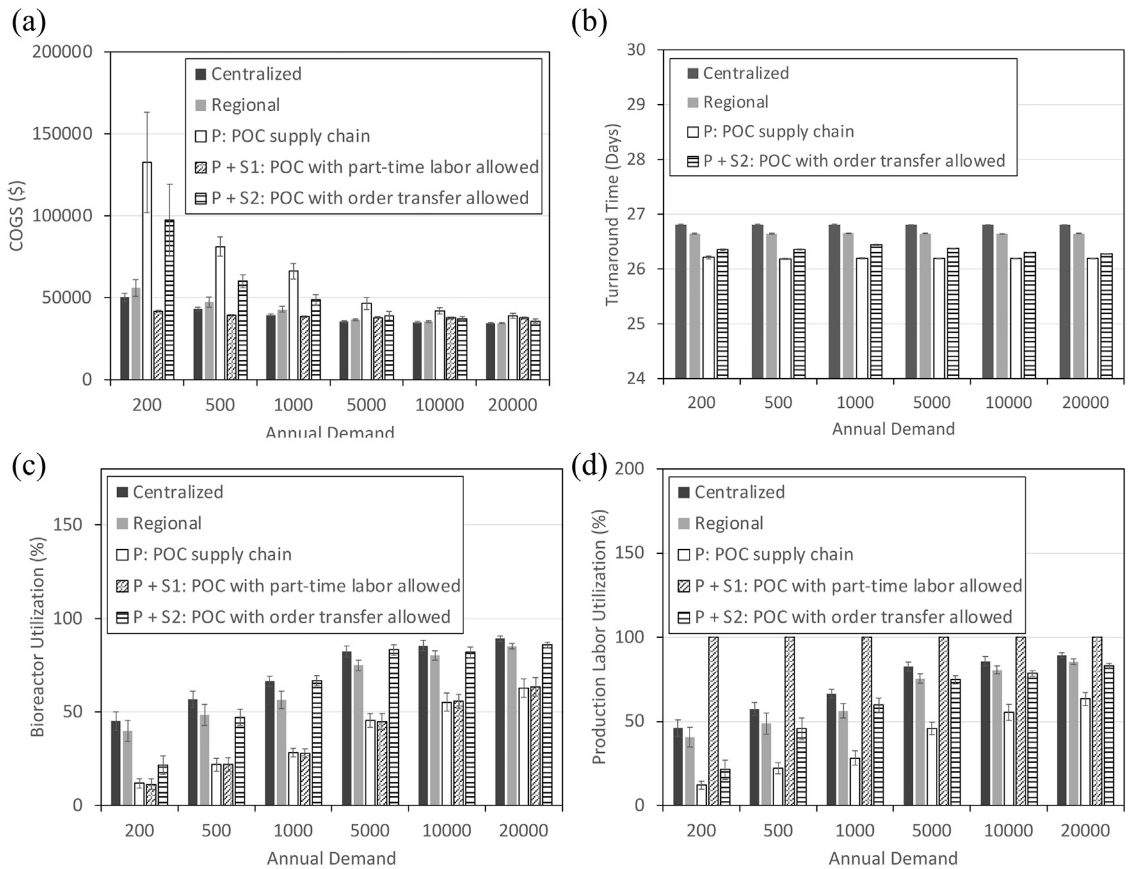

Figure 4. Comparison of P (POC), P+S1, and P+S2 scenarios in (a) COGS; (b) turnaround time; (c) bioreactor utilization rate and (d) production labor utilization rate. COGS, cost of goods sold.

fulfillment time, the overall network could operate more efficiently. To implement the order sharing rule in the simulation, a procedure could be established whereby; when an order is generated at a POC site with no available bioreactor or qualified personnel, all other POC sites report their bioreactor and personnel availabilities. The order would then be transferred to the closest site with the largest available capacity (Scenario P+S2). The comparison of Scenarios P, P+S1 and P +S2 are shown in Figure 4. Note that the nature of the simulation algorithm has led to the results of Case P+S2 being generated under the assumption of a 100% service level, while all other cases maintain a service level of 95%.

Table 3 presents the percentage of cost improvement for P+S1 and P+S2. The results indicate that P+S1 effectively reduces the cost of goods sold. In contrast, P+S2 also improves cost efficiency, but it results in a 0.62% increase in fulfillment time, as shown in Table 2. These findings demonstrate the significant impact of P+S1 and P+S2 on cost and fulfillment time, providing valuable insights for decision-makers in the industry. The comparison of labor utilization and bioreactor utilization are presented in Table 4 and Table 5, respectively.

Discussion and Conclusions

In this study, we investigated the impact of centralized and POC strategies on various KPIs such as cost, fulfillment time, service level and resource utilization in the supply chain of AuCT products using an agent-based simulation. The results revealed that, for the current estimated demand level, the centralized supply chain strategy showed significant advantages in production costs and resource utilization. However, with a predicted increased demand in the near future, the POC strategy can partially close the gap in the cost and resource utilization disadvantage compared to centralized to a certain extent, thereby leveraging its advantages in more flexible investment strategies and shorter order fulfillment time. The selection of a

Table 3
Percentage of cost improvement from P+S1 and P+S compared with POC.

Demand	P + S1	P + S2
10	75%	29%
25	61%	31%
50	51%	32%
100	37%	24%
250	25%	22%
500	14%	16%
1000	5%	12%

POC, point-of-care.

Table 4
Percentage of production labor utilization improvement from P +S1 and P+S2 compared with POC

Demand	P + S1	P + S2
10	727%	76%
25	351%	106%
50	255%	112%
100	173%	62%
250	118%	63%
500	80%	42%
1000	58%	31%

POC, point-of-care.

Table 5
Percentage of bioreactor utilization improvement from P+S2 compared with POC.

Demand	P + S2
10	81%
25	117%
50	137%
100	94%
250	82%
500	48%
1000	37%

POC, point-of-care.

suitable capacity for a single POC site is crucial to the overall performance of the supply chain for the POC strategy. Furthermore, introducing policies designed based on the uniqueness of AuCT products and advantageous to the POC strategy can enable small- and medium-sized manufacturers to add POC, which may be viewed as regionalized manufacturing depending on the number of manufacturing centers, as a competitive option to the trade-off considerations. The current study does not fully address a dynamic regionalized model whereby distributed collection and initial processing facilities or final product cryobanks are placed at or near POC [8]. Manufacturers will likely explore these policies in the future. Having suitable supply chain strategies for both large and small manufacturers can create a healthier ecosystem for the entire industry.

It is important to acknowledge that the simulation utilized in this study serves as a simplified decision support tool, primarily employed for facilitating what-if analyses. Implementing the proposed policies within a real supply chain context involves numerous practical considerations. These policies are subject to various constraints. For instance, in the case of the order transfer policy in a POC setting, if it results in frequent transfers of orders to different POC sites, the original purpose and advantages of the POC strategy may become compromised. Furthermore, this approach introduces additional burdens to the overall system's quality assurance, as it entails an augmented risk of quality issues and failures associated with assurance of manufacturing and analytics comparability amongst sites and the increased transportation activities.

In addition to the cost, turnaround time and utilization factors addressed within the simulations of this study, several other considerations must be considered when selecting a supply chain strategy. One such crucial aspect is the establishment of an effective quality management system across all POC sites. Regardless of where the therapies are manufactured, adherence to the same Food and Drug Administration–approved protocol is imperative for the manufacturing process. Furthermore, the facility infrastructure, including clean rooms, equipment monitoring and environmental monitoring, must be certified to meet the production requirements of the therapies. Manufacturers typically gather manufacturing and analytical data for the purposes of tracking, trend analysis, and continuous improvement. However, data collection across multiple POC sites presents greater challenges compared with a centralized facility. Although manufacturing the therapy at the clinic may facilitate coordination with pre-administration assessments and conditioning regimens, managing the entire POC supply chain requires intensified system-level management efforts.

This research has promising avenues for future exploration in two key areas. Firstly, there is a need to simulate product quality and explore strategies that can effectively support either a POC supply chain or a hybrid supply chain design. This would involve investigating approaches that enhance product quality throughout the supply chain, ensuring consistency and adherence to regulatory standards. In addition, an intriguing aspect to explore is the comparison of resilience among various supply chain structures, considering the inherent risk of disruptions in this emerging industry. The simulation tool employed can serve as a valuable resource for conducting stress tests on different supply chain configurations, evaluating their performance under diverse disruption scenarios such as supply shortages, labor shortages, demand fluctuations, manufacturing disruptions, and transportation interruptions. Such research efforts will provide valuable insights for designing robust and adaptable supply chains within the context of this nascent industry.

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Author Contributions

Conception and design of the study: K. W., B. W., C. W., B. L. L., A. D. F. Acquisition of data: K. W., C.-Y. T., Z. L. Analysis and interpretation of data: K. W., C.-Y. T., Z. L. . Drafting or revising the manuscript: K. W., C.-Y. T., Z. L. C. W., B. W., B. L. L. All authors have approved the final article.

Declaration of Competing Interest

Bruec L. Levine reports personal fees from Akron, Avectas, Immuneel, Immusoft, In8bio, Ori Biotech, Oxford Biomedica, ThermoFisher Pharma Services, UTC Therapeutics, Vycellix and is a co-founder and equity holder in Tmunity Therapeutics (acquired by Kite Pharma) and Capstan Therapeutics, outside the submitted work.

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There is no conflict of interest for other co-authors.

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Supplementary materials

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