Cytotherapy, 2019; 21: 1081–1093

International Society
ISCT
Cell & Gene Therapy

A multiscale simulation framework for the manufacturing facility and supply chain of autologous cell therapies

KAN WANG[1], YI LIU[1,2], JUNXUAN LI[3], BEN WANG[1,3,4], REID BISHOP[3], CHIP WHITE[3], AMRITAVA DAS[5], AARON D. LEVINE[6], LINDA HO[6], BRUCE L. LEVINE[7,8] & ANDREW D. FESNAK[7]

[1]Georgia Tech Manufacturing Institute, Georgia Institute of Technology, Atlanta, Georgia, USA,[2]School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, Georgia, USA,[3]H. Milton Stewart School of Industrial and Systems Engineering, Georgia Institute of Technology, Atlanta, Georgia, USA,[4]School of Materials Science and Engineering, Georgia Institute of Technology, Atlanta, Georgia, USA,[5]Morgridge Institutes of Research, Madison, Wisconsin, USA,[6]School of Public Policy, Georgia Institute of Technology, Atlanta, Georgia, USA,[7]Center for Cellular Immunotherapies, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, and [8]Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Abstract

Background aims: Autologous cell therapy (AuCT) is an emerging therapeutic treatment that is undergoing transformation from laboratory- to industry-scale manufacturing with recent regulatory approvals. Various challenges facing the complex AuCT manufacturing and supply chain process hinder the scale out and broader application of this highly potent treatment. *Methods:* We present a multiscale logistics simulation framework, AuCT-Sim, that integrates novel supply chain system modeling algorithms, methods, and tools. AuCT-Sim includes a single facility model and a system-wide network model. Unique challenges of the AuCT industry are analyzed and addressed in AuCT-Sim. Decision-supporting tools can be developed based on this framework to explore "what-if" manufacturing and supply chain scenarios of importance to various cell therapy stakeholder groups. *Results:* Two case studies demonstrate the decision-supporting capability of AuCT-Sim where one investigates the optimal reagent base stocking level, and the other one simulates a reagent supply disruption event. These case studies serve as guidelines for designing computational experiments with AuCT-Sim to solve specific problems in AuCT manufacturing and supply chain. *Discussion:* This simulation framework will be useful in understanding the impact of possible manufacturing and supply chain strategies, policies, regulations, and standards informing strategies to increase patient access to AuCT.

Key Words: *autologous cell therapy, cell manufacturing, multiscale simulation framework, supply chain*

Introduction

Autologous cell therapy (AuCT) is an emerging therapeutic method that uses a patient's own cellular material to treat disease. AuCT has demonstrated appropriate safety and efficacy and received regulatory approval in a small number of cancers [1,2] and shown promising results in clinical trials for a number of other indications, including blood disorders [3,4] and autoimmune diseases [5,6]. The transition from clinical trials to commercial products in the field of AuCT is evolving rapidly because of its tremendous potential benefits for patients. There are currently 906 companies developing cell and gene therapies and tissue engineering products worldwide, with a total of 1028 clinical trials as of the end of 2018 [7].

The use of autologous cells can significantly reduce the risk of immune rejection and disease transmission [8] but at the cost of increasing the complexity of the manufacturing and supply chain process. As the AuCT product is patient-specific, a separate batch of cells is manufactured for each patient. A typical manufacturing process for AuCT starts by taking a cell sample from the patient in the clinic, then transporting these cells to a central manufacturing facility for manipulation. At the manufacturing facility, these cells undergo isolation, purification, expansion, harvest and

Correspondence: **Kan Wang**, PhD, Georgia Tech Manufacturing Institute, Georgia Institute of Technology, 575 14th Street, Room 1943, Atlanta, GA, 30318, USA. E-mail: kan.wang@gatech.edu

(Received 5 April 2019; accepted 15 July 2019)

ISSN 1465-3249
https://doi.org/10.1016/j.jcyt.2019.07.002

formulation. For a genetically modified cell product such as chimeric antigen receptor T cells (CAR-T), the cells will also undergo activation and gene delivery through viral transduction or electroporation before expansion. After formulation, these cells are tested and then released back to the clinic for administration to the same donor patient [9,10].

Unlike the scalable allogeneic therapies, which can be modeled after therapeutic monoclonal antibodies (mAbs) production with established business models and robust supply chains, ideal manufacturing and distribution approaches have not yet been fully determined for AuCT. Many current manufacturing facilities for autologous therapies are designed or tuned to deliver innovative products that will be used in carefully controlled clinical trials. Notably, the facilities that are affiliated with universities or research centers usually have responsibilities other than manufacturing autologous therapies. For example, it is common that a production facility of an academic medical center supports several clinical trials, including investigator-initiated clinical trials. These academic production facilities (APFs) have the flexibility to reconfigure manufacturing space to produce different types of cell products. However, a significant challenge is responding to changes with real-time information in industrial production scenarios. Everything in every process, including machine schedules, personnel allocations, and reagent usage, is scheduled significantly before the actual production starts. Pre-deployment planning is a strategy that helps accomplish multiple types of tasks on time, rather than an efficient, low-cost, consistent strategy for accomplishing the same type of task. Considering that AuCT is an entirely patient-specific product and the patient's condition is likely to change at any time, this strategy, which relies on pre-planned production and distribution, is even less flexible in an industry setting.

The few companies that produce Food and Drug Administration–approved commercial AuCT products, such as Novartis Pharmaceuticals Corporation, Gilead Sciences and Dendreon, use their own dedicated manufacturing facilities. Unlike academic production facilities, where different types of products keep the production process open for adjustment at any time, these industrial production facilities (IPFs) need to optimize the production process for a single or several similar products. At a much larger manufacturing scale, IPFs also need to develop a sophisticated supply chain network that can ensure reliable and on time deliveries to treatment facilities across the country or the globe. In addition, the difficulty of many operational aspects in AuCT production facilities drastically increase with scaling up, such as production scheduling, prioritization, inventory management and workforce management.

Many unique challenges exist in scaling up AuCT manufacturing (Box 1). At present, there are not many IPFs for AuCT, and there is thus still much room for exploration on the optimal configuration strategy. In this article, we propose the development of a simulation platform as the factory's digital twin to experiment with new configurations to help tackle these challenges.

Box 1. A list of challenges that differentiate AuCT manufacturing from conventional manufacturing problems. QC, quality control.

Unique Challenges in Scaling AuCT Manufacturing

1. Evolving manufacturing/QC procedures
2. Large intrinsic uncertainties and complex propagation of variability
3. Real-time interaction between patient status and production/distribution
4. Time-dependent product quality
5. Highly-personalized manufacturing process
6. Young industry (a few dominant suppliers, labor scarcity, heavy regulatory restrictions, etc.)

Challenges in scaling up AuCT manufacturing

The AuCT supply chain network is composed of manufacturing facilities, suppliers, clinics, transport of specimens from clinics to facilities and transport of therapies from facilities to clinics. Each facility comprises bioreactors (the manufacturing capacity), AuCT orders assigned to the facility, reagent and supply inventory and the skilled workforce. Scheduling and coordinating patients with spare production capacity at the manufacturing facility within the product shelf life can significantly increase the complexity for scaling out commercial production. As the production ramps up to meet national or even global demand, manufacturers must choose between a centralized or more decentralized manufacturing network to determine the optimal number and locations of the manufacturing facilities, as well as the functions and operations conducted at each facility [11]. A simulation platform could be a valuable support tool to understand how these decisions will affect the manufacturing capacity, which in turn affects the cost of these cell products. In addition, a simulation platform could be used to study how delays affect the quality of the cells and optimize the scheduling of these manufacturing and quality testing steps.

There is a need for real-time and efficient communication among clinics, manufacturers and reagent suppliers. Real-time interaction between the manufacturing facility and the health care staff will allow better prediction of product delivery date based on the current manufacturing capacity. For example,

if a patient's condition suddenly becomes unsuitable for AuCT, the clinic should immediately notify the manufacturer to cancel subsequent production to reduce the loss in terms of cost and manufacturing capacity, and the cancellation of this order may also result in subsequent changes in reagent requirements. Similarly, if the reagent supplier foresees a disruption, the manufacturer should be notified immediately to take appropriate action, which in turn will cause the clinic to adjust the patient's AuCT injection schedule. The complexity of interaction between parties in the AuCT supply chain network exceeds the interactions in supply chain networks of other existing industries. Although no analytic tool is available to address the complexity at this high level, it is feasible to capture this complex interaction with a multiscale simulation with built-in stochastic algorithms.

Currently, the critical reagents in the manufacturing process of AuCT rely on only a few or, in many cases, the high-risk situation of a single supplier. Other high-risk situations include a reagent supply disruption, which could result in reagent shortages or stock outs in all IPFs, significantly reducing yield and hence significantly reducing patient benefit. A simulation platform could assist in the evaluation of "what-if" scenarios and the preparation of risk mitigation strategies. The efficiency and cost of deploying any risk mitigation strategy can also be estimated by running computational experiments on the supply chain simulation.

According to the Regenerative Medicine Standards Landscape published by Nexight Group and Standards Coordinating Body, 60 existing standards were relevant for cell therapy process as of February 2018 [12]. However, many of these relevant standards lack a sufficiently specific or useful guide for AuCT commercial development. The lack of standards can create significant difficulties in converting clinical trial manufacturing process into a full-scale commercial manufacturing process [13]. A simulation platform for planning AuCT production will need to be flexible and have a high degree of freedom to allow the manufacturer to explore the impact of different standards on their manufacturing process. A simulation platform can support a policy-maker with information such as how a policy affects the efficiency and the robustness of the supply chain.

Currently, there exist a few studies on analytic or empirical modeling for the cost of cell therapy manufacturing [11,14–20]. Although these studies provide valuable information regarding the economics of cell manufacturing process, none of them provide information detailed enough to address issues specific to a single AuCT facility, let alone the interactions between multiple facilities and different stakeholders. A simulation-based tool may serve better than oversimplified models in most decision-making scenarios. However, no such simulation tool can be found in the current literature. We developed a three-level (clinics, manufacturing facilities, and suppliers), two-scale (facility and supply chain network), stochastic simulation model. This model may be used as a decision support system (DSS) for the AuCT supply chain in service to manufacturers, health care providers, and ultimately patients.

Digital simulation framework for AuCT manufacturing (AuCT-Sim)

The proposed simulation framework has an array of key features to address the unique challenges expounded in the previous section. These features include a multiscale structure, multiple key performance indicators (KPIs), stochasticity when appropriate and a highly customizable framework. These features reflect the minimum requirements to capture the complexity of the AuCT supply chain problem. Sophisticated functions can be built on the basic framework to solve specific cases. The design of the computational experiment depends on the specific users' considerations of pinch points in sourcing, production, and delivery.

Multiscale structure

The most fundamental difference between the AuCT supply chain problem and conventional supply chain problems is that the AuCT supply chain model must include both the "microscale" activities inside a cell manufacturing facility and the "macroscale" interactions at the supply chain network level. In a conventional supply chain problem, the manufacturing facility and the supply chain network can be modeled separately because the products produced in the manufacturing facilities are interchangeable. Therefore, the manufacturing nodes in a conventional supply chain network model can be treated as "black boxes" where the detailed manufacturing procedures can be modeled with a separated simulation. However, in the AuCT supply chain problem, each product is linked with an individual patient. It is a truly build-to-order supply chain for a bespoke product. The patient's condition can influence timing of production and quality control procedures. Moreover, the patient is not only the consumer of the product but also the supplier of the raw material. If the manufacturing process of any product fails due to any reason, a request for a new specimen may be issued from the manufacturing facility to the clinic. Therefore, in a simulation run, it is essential to ensure real-time communication between the

manufacturing facility level and the supply chain level, which requires the model to contain both the micro and the macro scales.

Microscale simulation

The microscale simulation reflects any activities inside a manufacturing facility. The primary subsystems in a cell manufacturing facility include manufacturing procedures (Figure 1a), quality control procedures, inventory management and resource management. Figure 1b shows the interface of the microscale simulation platform. The specimens from clinics arrive at the top-left corner and go through the acceptance check and the upstream processing. Then the specimens enter a queue, waiting for bioreactors, operators and reagents to be assigned by the resource management subsystem. After the necessary resources are allocated, the specimens come to the expansion stage, where several quality control tests will be performed at different time points over the entire course. After the expansion, the products go through the downstream processing and release check subsequently. Qualified products are packed and distributed to the clinics for administration, which can be the same or different clinics from the ones where the specimens were collected. If the product fails any of the acceptance check, quality control tests, or the release check, the facility may request a new specimen to be sent from the patient. If the patient becomes unsuitable for treatment, a signal will be triggered and abort/pause the corresponding manufacturing process. The inventory management subsystem governs the replenishment of reagents and supplies.

Many communication ports exist at various components in this facility to ensure timely interactions with events at the macroscale level. The primary inlet port is at the arrival dock where the requests and specimens sent from clinic nodes are accepted. The primary outlet port is at the pack and distribution dock where the products are sent back to the requesting clinics. Every specimen in the facility also has a

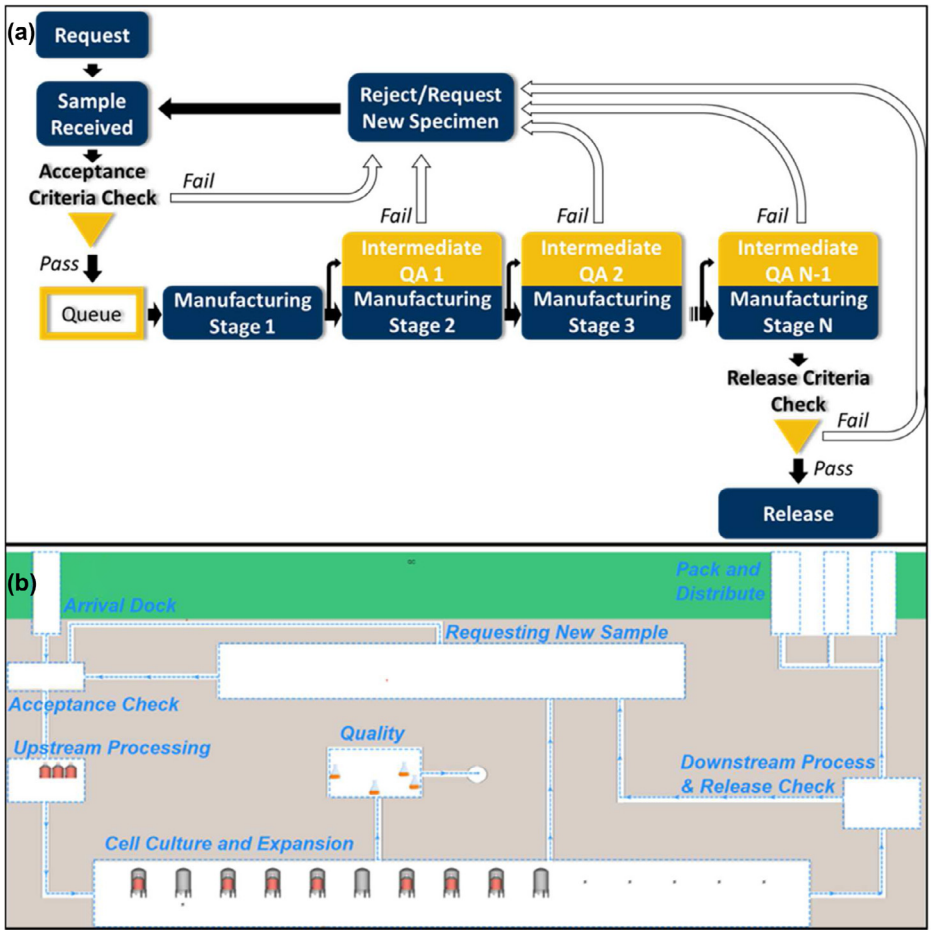

Figure 1. (a) The flow chart of activities inside a typical autologous cell therapy (AuCT) manufacturing facility. There are several windows for intermediate quality assessments (QAs). The manufacturing stages in this chart are groups of events in the manufacturing process separated by the intermediate QAs. They are not necessarily corresponding to actual manufacturing steps. (a) The simulation interface that monitors the internal activities of an AuCT manufacturing facility. After each manufacturing stage, a portion of the product is collected as samples for the QA. The rest will enter the subsequent manufacturing stages.

categorical variable, "Patient Status," that links to the status of the patient. Our framework handles a variety of specimens with patient categories using different actions regarding to their manufacturing process. A full list of "Patient Status" is included in the supplemental material. Our modeling framework (AuCT-Sim) models real-time patients' status changes using a state transition dynamic mechanism with a Markovian property. This structure assumes that patients' state changes are mutually independent, and patients would transit to states that are highly correlated with their health status. In this way, AuCT-Sim simulates real-time changes of patients whose specimens have arrived in the facility for production uses.

Beyond the dynamic of "Patient Status," AuCT-Sim also models the dynamic of specimen quality. Each specimen also has its own "Quality Check" categorical variable that may take a value among "Pass," "Fail" and "Pre-certified." A full list of these values as well as operations associated with specimens in such categories are summarized in the supplemental material. Any product that fails a quality check cannot be replaced by another product, a new request for the patient's specimen is necessary whenever the value of this variable changes to "Fail." The change happens when a quality control procedure is performed.

Justifications of quality failure in AuCT-Sim rely on a "Quality" index valued as real numbers between 0 and 1, where 1 indicates that the product is in its "perfect" state and 0 indicates the product is totally unusable. We assume that the initial quality of the specimen follows a predefined distribution upon its arrival. As the quality of the specimen may deteriorate over time (e.g., the viability of the cells may decrease overtime during production), the "Quality" index of the specimen will decrease at a random rate. The exact decreasing value at each time step is sampled from a distribution that can be deduced from empirical knowledge. This deterioration can be the result of cells failing to expand, or the loss of sterility, viability and potency during production. For example, whenever the product is exposed with the outer environment (e.g., to take samples for quality control tests or to be transferred from one container to another), there is a small chance that contamination may happen, and hence "Quality" will be set to 0. The probabilities of contamination at each manufacturing and quality control procedure preset based on empirical data. In any quality control test, the value of "Quality" will be compared against a preset criterion of that test. Once the "Quality" index is lower than required, the value of "Quality Check" changes to "Fail"; otherwise, the "Quality Check" stays the same.

The inventory management subsystem has a communication port that links to supplier nodes in the supply chain network. Multiple inventory replenishment policies can be pre-programmed. The subsystem can switch between different policies based on a certain global event. For example, the reagent suppliers may forecast a supply change. The manufacturing facilities in the affected distribution region may switch to a more conservative reagent replenishment policy.

Similarly, the resource management subsystem can also communicate with events outside of the facility. In a case of demand surge (which may be caused by a new indication approval or reimbursement allowance, for example), the facility may ask the operators to work overtime until more operators are recruited. There are also communication ports at each quality control step, as they could be outsourced under certain circumstances.

It should be noted that the microscale simulation of a single manufacturing facility can be packaged into a standalone tool. For example, the demand from clinics can be simulated by a Poisson process or extracted from historical data. Similarly, other communication ports can be fed by random number generators or historical data. The standalone manufacturing facility tool could be used to support decision-making at the microscale. Examples of such decisions include the following:

- What is the bottleneck of the production capacity?
- What is the relationship between manufacturing configurations and batch capacity and turnaround time?
- How does a manufacturing innovation impact patient benefit?

Macroscale simulation

The macroscale simulation is designed to model the allocation of multiple manufacturing facilities, which can have different configurations at the microscale level, and the connection with clinics and suppliers as a supply chain network. Figure 2 shows the three archetypes of the supply chain network designs: the centralized production model, the regional manufacturing hubs model, and the "point of care" production model. There can also be hybrid solutions that use more than one basic design type in different regions or under different situations.

The macroscale simulation for supply chain can generate valuable information related to the entire AuCT industry or the entire AuCT supply chain network. A few typical questions that could be answered by this tool are the following:

- What are the strengths and weaknesses of each of the three supply chain network designs?

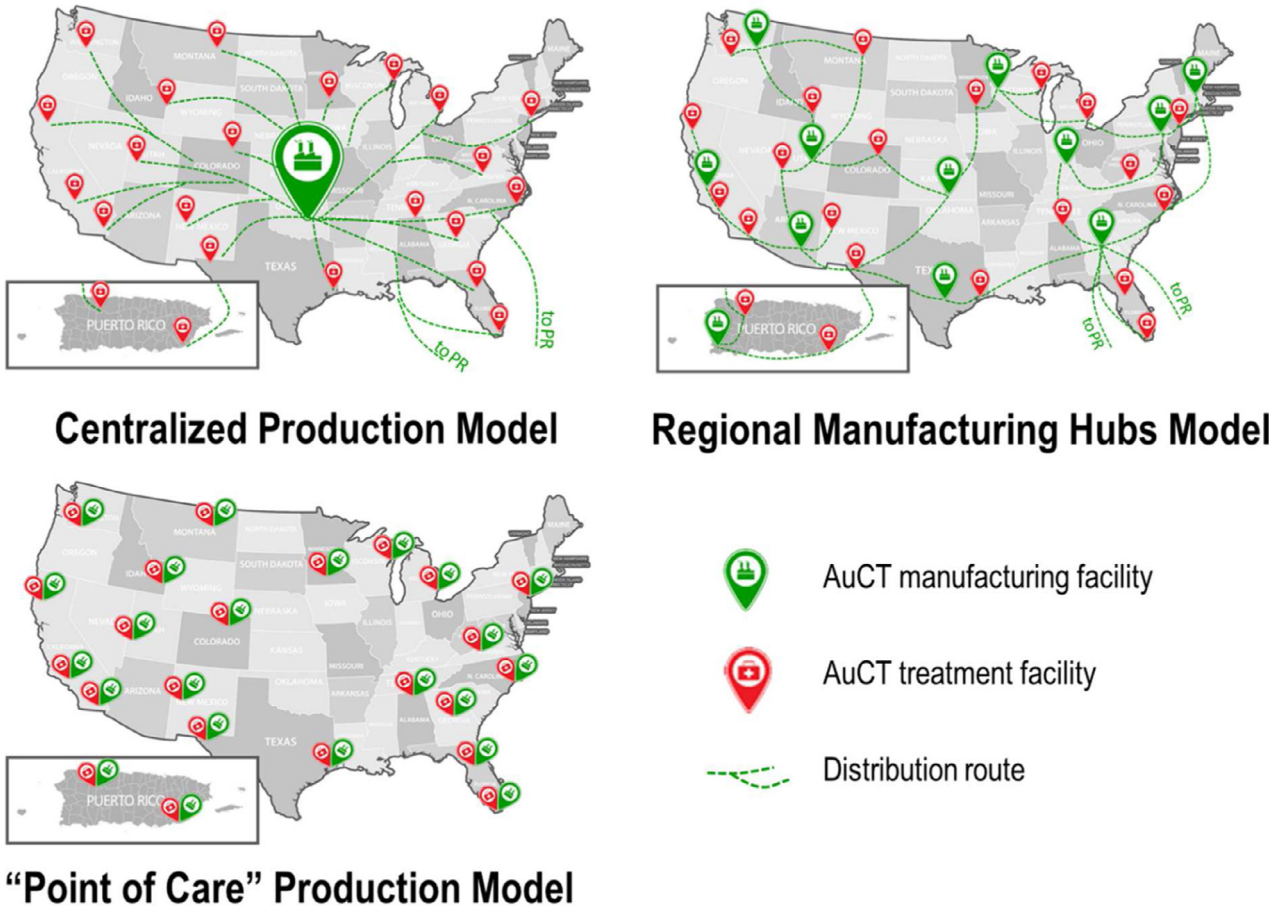

Figure 2. Three supply chain network designs: the selection of network design depends on many factors, including the distribution of demands and resources, the costs to ensure the quality consistency at different manufacturing sites, and patient accessibility, among others.

- What are the optimal number and placement of manufacturing facilities given specific demand distribution over the country or globally?
- What are the risk mitigation strategies to counter an unexpected event, such as a reagent supply disruption, and what are the costs and performance of these strategies?
- How will policies and regulations affect the efficiency and the robustness of the supply network?

Multidimensional key performance indicators

The AuCT-Sim generates and records comprehensive manufacturing and distribution data from each simulation run. The statistical indicators output can be divided into three subgroups: time, efficiency and cost. Different stakeholders may have different weighting factors assigning to these indicators when evaluating the overall performance.

Time-related indicators

The fulfillment time is composed of manufacturing time and distribution time, each indicates the performance of the manufacturing facility and the supply chain network, respectively. The manufacturing time is the time between when the specimen arrives the manufacturing facility and when the product leaves the facility for delivery. It can be further divided into four components: processing time, quality control time, queue time and outage time.

The processing time is the necessary time to produce the AuCT product, including upstream processing, cell expansion, and downstream processing. This component is insensitive to operational decisions.

The quality control time is the time spent on actions to ensure the quality of the product, including the acceptance check, the releasing check and the intermediate quality control assays. The acceptance check and the releasing check are done before and after the production process. The intermediate quality control steps are distributed at different time points during the production to prevent the risk of wasting resources on continuing processing products that have fallen below the necessary quality requirements. Figure 3 shows three strategies to arrange the in process quality control steps. On the basis of the relative importance of reducing production time and

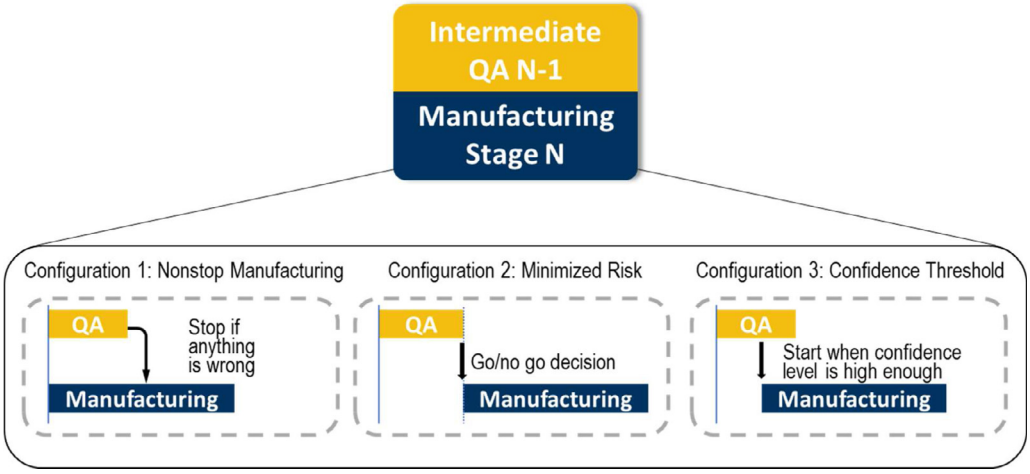

Figure 3. Different quality control strategies: one of the three configurations can be selected based on the trade-off between the total manufacturing lead time and the risk of wasting resources on products that have already failed in the preceding manufacturing stage.

reducing waste risk, decision-makers can make quality control steps and production steps overlap in time at different degrees. Therefore, the overall quality control time is partially controllable by the manufacturer depending on the configuration.

The queue time is primarily determined by the demand and the manufacturing capability of the facility. Different queuing policies can also have impacts on the average queue time. The goal of any manufacturing facility should be making the queue time as short as possible without reducing the utility of resources.

The outage time is the wasted time caused by various unexpected events, such as machine breakdown, power outage, reagent supply disruption, and so forth. One special case in cell manufacturing is contamination. Any operation involving the interaction of the product and the environment will bring the risk of contamination. The time previously spent on contaminated products is wasted. A new specimen must be requested, and the production must start over.

The distribution time is determined by the design of the supply chain network, which has different aspects including the amount and placement of manufacturing facilities, the methods and routes of delivery and the real-time conditions of transportation. The goal of optimization is to minimize the distribution time within the constraint of the total cost. Note that the total cost is affected by the cost of transportation and additional factors. For example, the location of a manufacturing facility determines the rent, tax and salary criteria of its employees. In practice, the location of a manufacturing facility is usually assessed by factors including the cost, patient accessibility, the demand distribution.

Efficiency-related indicators

The efficiency of the microscale model refers to the utility of machines, reagents, labor and spaces. Any idle resource implies a fraction of the cost that can be potentially reduced. However, because there is intrinsic uncertainty of the AuCT industry and the product is for therapeutic use, it is necessary to reserve some resources for contingencies. The optimal ratio of reserved resources is difficult to determine solely via use of the simulation model. Decision-makers can preset various scenarios to find the balance between reserved resources and uncertainty handling. Once the balance point is determined, the manufacturer can use the model to find a facility setting that can achieve the desired utility of different resources. The effects of various disaster scenarios can also be verified using the simulation model.

At macroscale, the efficiency refers to the fulfillment rate of a facility and the marginal utility of a new manufacturing facility at a specified location. Specifically, it measures the increase in the patient benefit, especially patient accessibility, caused by adding a new manufacturing facility. The efficiency of the supply chain network is low if the service areas of many manufacturing facilities substantially overlap.

Cost-related indicators

The AuCT-Sim collects cost data for each product during the simulation run and uses the data to calculate two cost indicators: “cost per batch” and “cost per year.” A detailed breakdown of the cost tracked in the model can be located in the supplementary material.

Table 1 is a summary of all indicators that compose the output of the AuCT-Sim. Because different users may have different emphasis on these indicators,

Table 1. Key performance indicators calculated by the simulation model.

Category	Key performance indicator	Relevant Stakeholders							
		Patients	Manufacturers	Health care Providers	Researchers	Regulators	Policymakers	Employees	Reagent supplier
Time	Fulfillment time	✓	✓	✓	✓	✓	✓		
	> Manufacturing time	✓	✓	✓		✓			
	> > Production time		✓						
	> > Quality control time		✓			✓			
	> > Queue time	✓	✓	✓					
	> > Down time		✓						
	> Distribution time		✓	✓			✓		
Efficiency	Machine utility		✓					✓	
	Labor idle time		✓						
	Reagent reserve		✓						✓
	Unused inventory space		✓						
	Fulfillment rate	✓	✓	✓					
	Increased service coverage	✓	✓				✓		
Cost	Cost per batch	✓	✓	✓			✓		
	Cost per year		✓				✓		

the key performance indicator is essentially a multidimensional variable with user-assigned weighting factors. The AuCT-Sim's task is to provide comprehensive information for the user to make the decision.

Stochastic settings and highly customizable framework

AuCT-Sim framework is able to model a large number of stochastic processes in cell manufacturing. These processes include patient demand arrival process, patient health status transition process, specimen viability decay process, cell deterioration/pollution process and production equipement ON–OFF process. All the processes are highly customizable and allow the user to modify many parameters before and during each simulation run. These settings may be changed according to the historical data from the specific facility. Alternatively, the historical data can be used directly as the input with a tabular format. Case studies may also be developed with the AuCT-Sim by modifying various aspects, such as the amount and placement of the clinics, manufacturing facilities and the reagent suppliers, the route of manufacturing and quality control procedures, the fluctuation in demand and supply, and the quality control thresholds.

Simulation model validation

Simulation model validation is the task of demonstrating that the digital twin is an equitable or reasonable representation of the actual manufacturing facility. The AuCT-Sim framework provides animation and output statistics for the users to validate their simulation testbeds, which ensures that by analyzing the simulation model researchers can gain insights about their system designs without costly and time-consuming physical trial and error. Validation approaches to simulations include subjective expert reviews and objective input-output statistical tests [21]. We suggest a three-step validation routine [22] to validate the simulation models produced by AuCT-Sim:

1. Cell-manufacturing process experts who are knowledgeable with the system review the validity of this simulation model based on the model animation; this system animation demonstrates manufacturing details, including the production flow from specimen arrival to final shipment, the consuming/replenishing of reagent inventory, the use and release of recyclable recourses (bioreactors and technical operators), the failure and repair of bioreactors and all quality control sampling and testing.

2. Validate model assumptions: All key assumptions must be revealed to review by subject matter experts for a validation check. For assumptions related to input data/distribution(s), implementers should collect related data for statistical tests.
3. Output analysis: Output from the system was compared with model outputs with an identical set of input conditions. Given the validated input parameter(s)/distribution(s), the simulation output should not be significantly different from physical system output. With data collected from both the simulated and the physical production systems, the implementers should conduct a nonparametric statistical test to examine the similarity between the two systems. Wilcoxon signed rank test and Mann-Whitney *U* tests are two commonly used methods to investigate statistical similarity or significant difference.

We note that we do not have data access to an AuCT commercial production system, in part because that the industry is in an early phase of development. However, once real production data become available, researchers and engineers will be able to validate a simulation model of their system, following the three-step validation guideline presented above. An example of a simulation model validation with a hypothetical facility is included in the case study section.

Demonstrative case studies

A virtual CAR-T manufacture facility was built based on system specifications collected from an conceptual AuCT production facility that is in the phase of designing. Detailed parameters of the simulation can be found in the supplementary material.

Case 1: Choose an appropriate reagent base stock level

The objective of this case study was to determine a good periodic reagent replenishment policy to reduce the possibility of a stock-out while also reducing the likelihood of having excess reagent in inventory. We restricted our interest to a *base-stock* replenishment policy (or order-up-to policy), where periodically we place an order for reagent units that equals the base-stock level (the design parameter), minus the number of units of reagent in inventory. For example, for base-stock level B and current reagent inventory level R, the amount of reagent to order is $B - R$, if $B - R$ is non-negative (otherwise, do not order). Base-stock replenishment policies are optimal for a large class of nonperishable inventory systems and usually are excellent suboptimal policies for perishable inventory systems.

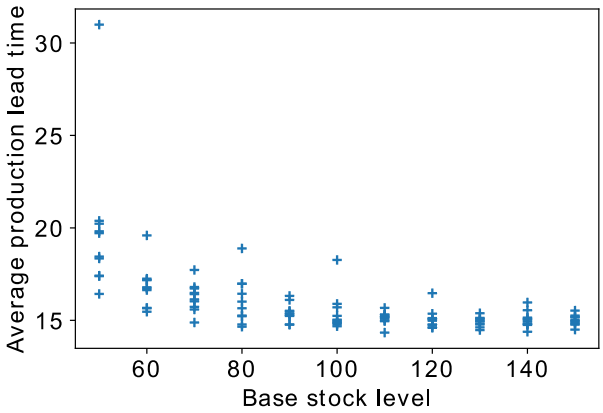

Figure 4. Base stock level versus average production lead time. The average production lead time is monotonically decreasing as the base stock level increases. Typically, the decrease becomes modest once the base stock level exceeds certain threshold amount (120, in this case).

In the simulation, we treat the batch of all needed reagents as a single unit of reagents. All other system specifications were fixed, while the base stock level was varied from 10 to 150 in 10 step increments. Each base stock level is tested 10 times with randomly generated starting seeds. To ensure appropriate comparison across different base stock levels, we group each of the 10 times of simulations with different base stock levels as a master replication. The starting seed of each master replication must be kept identical to ensure that all event scenarios are the same except the variable of our interest (base stock level). One hundred and ten data points collected from AuCT-Sim are scattered in Figure 4. The figure shows that the average production lead time is monotonically decreasing as the base stock level increases and that this decrease becomes quite modest once the base stock level exceeds 120. Our interpretation of these data is as follows: (i) there is little value in a base stock level greater than 120 to decrease the average production lead time, (ii) there is little reason to have a base stock level greater than 120 to reduce the possibility of an excess(and expensive) amount of reagent units in inventory, and hence (iii) 120 appears to be a reasonable choice for a base stock level.

Case 2: Mitigating the risk and impact of supplier disruption

The target of this research case study was to investigate several system performances when a supplier disruption occurred and later recovered, with different combinations of the bioreactor and technical operator quantities. The system can then assist the designer in determining how many bioreactors and operators are needed to mitigate the risk of supplier disruption. Supplier disruption is a likely and severe

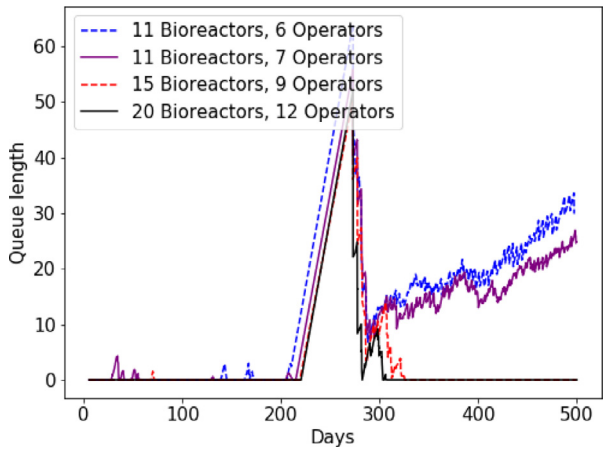

Figure 5. Trends of queue lengths for different facility designs: for each facility, the queue length of the facility increases after the supplier disruption occurred on day 200; and the queue length diminishes after resuming the reagent supply on day 260.

risk for biomanufacturers. In 2017 alone, the cell therapy industry witnessed a saline shortage due to Hurricane Maria and a severe flu season [23,24], as well as the shutdown of a major cell therapy supplier due to sterility issues [25]. We are interested in how the system performance recovers after the occurrence of supplier disruption.

Figure 5 depicts queueing lengths of different facility designs over the horizon of 500 days. Queue lengths of every facility increased after the supplier disruption occurred on day 200; and queue lengths diminish after resuming the reagent supply on day 260. The facilities with 20 bioreactors and 12 operators (black line) and with 15 bioreactors and 9 operators (red dotted line) are able to recover to the normal state within 42 and 64 days, respectively. In contrast, the facilities with 11 bioreactors and 7 operators (purple line) and with 11 bioreactors and 6 operators (blue dotted line) fail to recover after the reagent disruption. Moreover, facilities with an insufficient number of bioreactors or operators would also lead to further increases in specimen queue lengths after the disruption ended since the constrained number of bioreactors would not able to clear the requests accumulated during the disruption period.

Figure 6 summarizes a few of the KPIs used to evaluate system performances for cases with 11

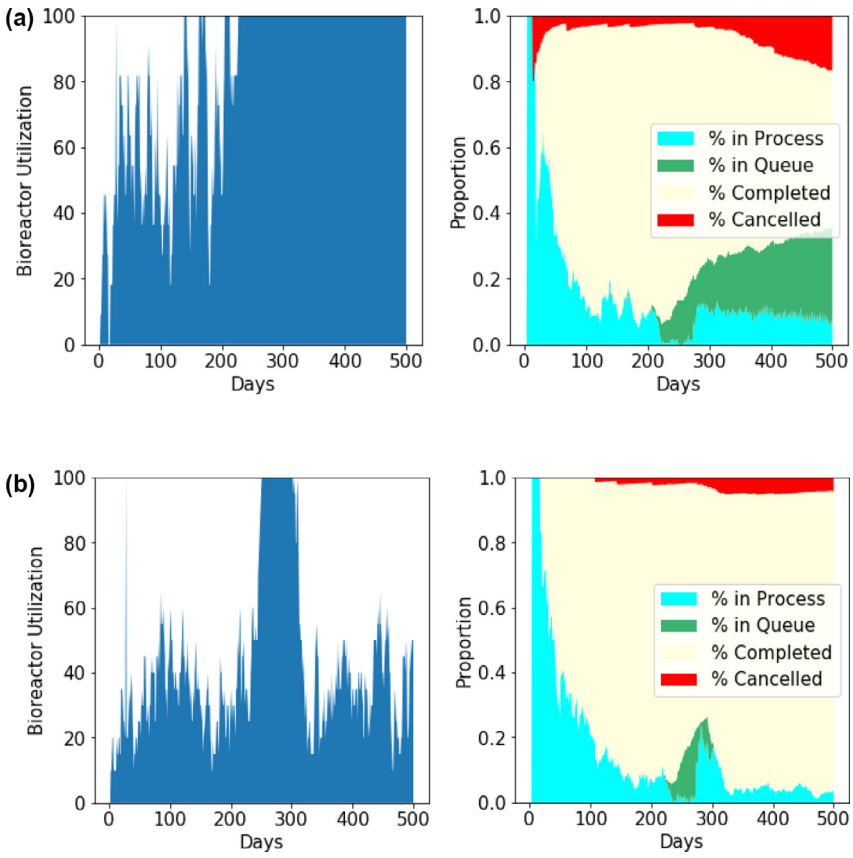

Figure 6. System performance under selected equipment and labor force specification: two configurations are selected for the comparison. Additional testing details are included in the supplementary material. (a) Eleven bioreactors and six operators. (b) Twenty bioreactors and twelve operators.

bioreactors and 7 operators (6A) and 20 bioreactors and 12 operators (6B). Additional testing details are included in the supplementary material. As shown in Figure 6a, when 11 bioreactors and 7 operators are equipped, the supply chain fails to recover after the supplier disruption from Day 200; the bioreactor utilization is kept at 100%; and the proportion of patients who canceled their production increases eventually to nearly 20%. The proportion of patient queued also increases to 37% by the end of Day 500.

For the system equipped with sufficient bioreactors and operators (20 bioreactor and 12 operators in Figure 6b), bioreactor use rate recovers to normal on Day 334. The proportion of patients who canceled their production increased only by 3% and then mildly recovers to normal by the end of the testing period. The proportion of patients in the queue increases to 29% after the disruption occurred but then recovers quickly to normal by day 320.

By carefully tuning bioreactor and operator quantities, the decision maker can visualize the recovery ability under given system specifications and design strategies to mitigate the risk to process disruption.

Testbed validation

Step 1: Check face validity

The simulation tool we developed compiles a system animation automatically for expert review. This system animation demonstrates manufacturing details, including the production flow from specimen arrival to final shipment, the consuming/replenishing of reagent inventory, the utilization of bioreactors and technical operators, the failure and repair of bioreactors, and all quality control sampling and testing. An expert team is involved to validate the logistics of the simulation animation to check face validity.

Step 2: Validate model assumptions

We list the following key assumptions of the simulation model produced by AuCT-Sim framework: (i) Patient specimens are independent (i.e., specimen occurrence, specimen pollution and patient mortality are not correlated); (ii) bioreactors' operations are independent (i.e., bioreactor failures are independent, and bioreactor recoveries are independent); and (iii) therapy requests occurred according to a Poisson process.

All key assumptions are revealed to the expert review team for validation check to make sure that none of the assumptions violate expert intuitions or practical wisdoms.

Step 3: Output analysis

For the conceptual system, the only data we have confirms with system experts is that the production failure rate is roughly 5%. We collect failure rates of the simulation model from 100 simulation tests (see Figure 7 for the empirical distribution of the simulation system's production failure rate).

One sample Wilcoxon signed rank test is performed to test if the failure rate yielded by our simulation model equals 5%. The P value of Wilcoxon signed rank test is 0.7027, which indicates that the output of the simulated system has no significant difference with the system specifications provided by the facility expert. We have thus statistically validated that the simulation system produced by our framework is a good representative of the conceptual facility having similar input–output relation.

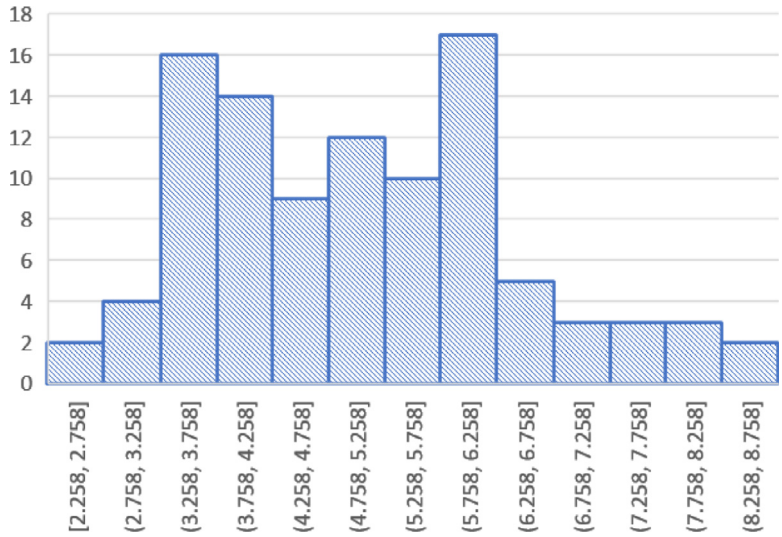

Figure 7. Histogram of production failure rates (100 tests).

Discussion

As an emerging industry, AuCT manufacturers must engage in data-driven planning before expansion. However, high uncertainty, the steep upfront investment and the lengthy trial duration make practical verification of planning scenarios impractical. Running computational experiments with a simulation model becomes an economical alternative for several reasons.

First, the AuCT-Sim generates and records data comprehensively with perfect repeatability. In real-life experiments, some critical data could be overlooked at the beginning due to the lack of fundamental knowledge. With computational experiments, all data are stored and can be regenerated. Although some parameters are stochastic, recording the seed of the random number generator ensures that repeats generate the same "random" values.

Second, factors in the AuCT-Sim are controllable. In real-world manufacturing demonstrations, it is challenging, if not impossible, to isolate one particular factor from numerous factors in an AuCT manufacturing facility to test its effect. The effect can be confounded with the considerable variability in other factors. With simulation, it is easy to vary one factor in multiple computational experiments to evaluate its actual effect.

Third, the AuCT-Sim can be used to investigate hypothetical scenarios. The simulation can provide insights into events that are too large in scale to set up a real-life experiment, such as a hurricane-caused reagent supply disruption that affects the entire east coast of the United States. Decision-makers can use this DSS to test different risk mitigation strategies and be prepared to counter similar events in the future.

Fourth, the AuCT-Sim can highlight and clarify ethical trade-offs inherent in the complex CAR-T cell manufacturing processes. The focus of supply chain optimization is typically and understandably meeting anticipated demand while minimizing the cost of goods. Decisions about the number of manufacturing facilities to use, their locations and their capacity, among many other factors also affect the extent to patients or subsets of patients can access a specific therapy safely, reliably and in a timely manner. Such information is critical to firms developing strategies to scale their production and incorporating potential contingencies into their planning processes. Supply chain simulation, combined with information on the possible size, location and prognosis of patient populations, in particular, may offer a uniquely powerful approach to identify proactively concerns relevant to the commercialization of novel cell therapies early in the development process and proactively address them.

Because the framework is highly customizable, it is a versatile tool that can help with the study of various subjects. Future research directions following this work include the following:

- What is the optimal patient priority policy for compassionate care cases?
- What is the best transshipment strategy for the robustness of the supply chain network?
- Which inventory replenishing policy is the most suitable for an AuCT facility, considering the possibility of supply disruptions?
- How to make policies to encourage manufacturers to expand into regions with low patient accessibility?
- What are the marginal effects of technical innovations in different manufacturing and quality control procedures?

Acknowledgments

This research is supported by funds from the Marcus Foundation, the Georgia Research Alliance and the Georgia Tech Foundation through their support of the Marcus Center for Therapeutic Cell Characterization and Manufacturing (MC3M) at the Georgia Institute of Technology. This material is also based on work supported by the National Science Foundation under grant no. EEC-1648035. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation.

Disclosure of interests: Bruce L. Levine reports personal fees from Avectas, Brammer Bio, Incysus, CRC Oncology/Cure Genetics, Novartis, Terumo and Draper Labs and is a co-founder and equity holder in Tmunity Therapeutics, outside the submitted work. The other authors have no commercial, proprietary or financial interest in the products or companies described in this article.

References

[1] Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science 2015;348:62–8. https://doi.org/10.1126/science.aaa4967.

[2] June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. Science 2018;359:1361–5. https://doi.org/10.1126/science.aar6711.

[3] Ribeil J-A, Hacein-Bey-Abina S, Payen E, Magnani A, Semeraro M, Magrin E, et al. Gene Therapy in a Patient

with Sickle Cell Disease. N Engl J Med 2017;376:848–55. https://doi.org/10.1056/NEJMoa1609677.

[4] Thompson AA, Walters MC, Kwiatkowski J, Rasko JEJ, Ribeil J-A, Hongeng S, et al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med 2018;378:1479–93. https://doi.org/10.1056/NEJMoa1705342.

[5] Ellebrecht CT, Bhoj VG, Nace A, Choi EJ, Mao X, Cho MJ, et al. Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. Science 2016;353:179–84. https://doi.org/10.1126/science.aaf6756.

[6] Miyara M, Ito Y, Sakaguchi S. TREG-cell therapies for autoimmune rheumatic diseases. Nat Rev Rheumatol 2014;10:543–51. https://doi.org/10.1038/nrrheum.2014.105.

[7] Lambert J. Alliance for Regenerative Medicine. State of the Industry 2019 https://alliancerm.org/wp-content/uploads/2019/01/State-of-the-Industry-2019-FINAL.pdf.

[8] Kazmi B, Inglefield CJ, Lewis MP. Autologous cell therapy: current treatments and future prospects. Wounds 2009;21:234–42.

[9] Levine BL, Miskin J, Wonnacott K, Keir C. Global Manufacturing of CAR T Cell Therapy. Mol Ther Method Clin Dev 2017;4:92–101. https://doi.org/10.1016/j.omtm.2016.12.006.

[10] Bartel RL. Stem Cells and Cell Therapy: Autologous Cell Manufacturing. In Translational Regenerative Medicine. Academic Press; 2015. p. 107–12. https://doi.org/10.1016/B978-0-12-410396-2.00008-6.

[11] Harrison RP, Rafiq QA, Medcalf N. Centralised versus decentralised manufacturing and the delivery of healthcare products: A United Kingdom exemplar. Cytotherapy 2018;20:873–90. https://doi.org/10.1016/j.jcyt.2018.05.003.

[12] Nexight Group, Standards Coordinating Body. Summary of existing regenerative medicine standards. The Regenerative Medicine Standards Landscape February 2018 https://www.standardscoordinatingbody.org/landscape-report-release.

[13] Markowitz-shulman A, Addie S, Hackmann M, Alper J, Beachy SH. Navigating the Manufacturing Process and Ensuring the Quality of Regenerative Medicine Therapies. Washington, DC: National Academies Press; 2017. https://doi.org/10.17226/24913.

[14] Abou-El-Enein M, Römhild A, Kaiser D, Beier C, Bauer G, Volk H-D, et al. Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: a novel tailored model for optimizing performance and estimating costs. Cytotherapy 2013;15:362–83. https://doi.org/10.1016/j.jcyt.2012.09.006.

[15] Simaria AS, Hassan S, Varadaraju H, Rowley J, Warren K, Vanek P, et al. Allogeneic cell therapy bioprocess economics and optimisation: Single-use cell expansion technologies. Biotechnol Bioeng 2013;111:69–83. https://doi.org/10.1002/bit.25008.

[16] Jenkins MJ, Farid SS. Cost-effective bioprocess design for the manufacture of allogeneic CAR-T cell therapies using a decisional tool with multi-attribute decision-making analysis. Biochem Eng J 2018;137:192–204. https://doi.org/10.1016/J.BEJ.2018.05.014.

[17] McCollister KE, Leff JA, Yang X, Lee JD, Nunes EV, Novo P, et al. Cost of pharmacotherapy for opioid use disorders following inpatient detoxification. Am J Manag Care 2018;24:526–31.

[18] Lopes AG, Sinclair A, Frohlich B. Cost Analysis of Cell Therapy Manufacture Autologous Cell Tharapies, Part 2. Bioprocess Int 2018.

[19] Lopes AG, Sinclair A, Frohlich B. Cost Analysis of Cell Therapy Manufacture Autologous Cell Tharapies, Part 1. Bioprocess Int 2018.

[20] Harrison RP, Zylberberg E, Ellison S, Levine BL. Chimeric antigen receptor-T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods. Cytotherapy 2019. https://doi.org/10.1016/j.jcyt.2019.01.003.

[21] Sargent RG. Verification and validation of simulation models. J Simul 2013;7:12–24. https://doi.org/10.1057/jos.2012.20.

[22] Naylor TH, Finger JM. Verification of computer simulation models. Manage Sci 1967;14:B96–B106. https://doi.org/10.1287/mnsc.14.2.B92.

[23] Jarvis LM. Hurricane Maria's lessons for the drug industry. Chem Eng News 2018;96 https://cen.acs.org/pharmaceuticals/biologics/Hurricane-Marias-lessons-drug-industry/96/i37. [Accessed February 26, 2019].

[24] Wendelbo M, Blackburn CC. A Saline Shortage This Flu Season Exposes a Flaw in Our Medical Supply Chain. Smithsonian.com 2018 https://www.smithsonianmag.com/innovation/saline-shortage-this-flu-season-exposes-flaw-in-our-medical-supply-chain-180967879. [Accessed February 26, 2019].

[25] Lonza Palmer E. U.S. cell therapy plant slapped with FDA warning letter. FiercePharma 2017 https://www.fiercepharma.com/regulatory/lonza-u-s-cell-therapy-plant-slapped-fda-warning-letter. [Accessed February 26, 2019].

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2019.07.002.