CELL & GENE THERAPY INSIGHTS

SUPPLY CHAIN FOCUS: GLOBAL COMMERCIAL STRATEGIES

EXPERT INSIGHT

Supply chain challenges and issues facing the autologous cell manufacturing industry

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We discuss three supply chain challenges and issues facing the autologous cell manufacturing industry that may impact patient outcome and supply chain performance in a commercial setting. These are (i) the potential value of giving priority to the sickest patients with respect to the start of manufacturing their therapy, (ii) determining the optimal manufacturing capacity and reagent replenishment policy for a single cell manufacturing facility, given demand forecasts and patient service levels, and (iii) the resilience of reconfigurable supply chain networks for supply chains with geographically distributed manufacturing capacity.

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Autologous cell therapy, a new form of personalized medicine, is an emerging therapeutic method where a patient's own cells are used as medical treatment. In one prominent example, T cells are bioengineered to express chimeric antigen receptors (CARs) that identify, attach to, and subsequently kill tumor cells. These CAR-T cell therapies have proven highly effective for treating patients with life-threatening blood cancers. These successes, along with a wave of research and investment, suggest that autologous cell therapy is poised to play a key role in a new era of cancer care and to benefit

patients with a range of other medical conditions as well.

The resulting emerging industry and supplier base are generating new and important supply chain design and operations challenges. The NSF Engineering Research Center for Cell Manufacturing Technologies (CMaT) Center, headquartered at the Georgia Institute of Technology, is a translational research center dedicated to enabling the robust, scalable, low-cost biomanufacturing of high-quality therapeutic cells in order to bring affordable, curative therapies against incurable chronic diseases to as many individuals as possible. CMaT is currently supporting simulation-based studies, led by the authors, that aim to reduce total manufacturing and logistics cost and risks, improve patient benefits (with focus on improving patient safety, reducing mortality rate, and increasing access), and incorporate patient and regulatory perspectives. Details of several of these studies are described in [1].

A variety of supply chain challenges and issues facing the autologous cell manufacturing industry have received attention in the industry literature. A partial list of these challenges and issues includes: cost of goods [2,3], a variety of risks including raw and starting materials, quality, variability, demand surge, reagent supplier disruption [2,4–8], the need for flexible facility growth plan for increased capacity for future commercialization [2,9], procurement [10], the identification of Critical Quality Attributes [6], data management [11,12], upstream and downstream bio preservation [3], reagent inventory control [13], supply chain network design, i.e., centralized manufacturing capacity versus distributed [13], product consistency, automation, and distributed manufacturing capacity [13], firm structures in the industry, i.e., whether to outsource or depend on internal capabilities, the 'make or buy' decision, mergers and acquisitions [13–15], regulatory considerations [16], and workforce considerations [17]. We now elaborate on a few of these challenges and issues and address three in more detail – priority queuing, capacity planning, and reconfigurable supply chain network resilience – that in our opinion are emerging challenges and issues that have been insufficiently examined.

With regard to the cost of goods and other costs, cost is a major barrier to the broad accessibility of these immunotherapies [18]. Novartis' novel CAR-T cell therapy Kymriah has a list price of $373,000 or $475,000, depending on the type of cancer. Yescarta, a cell therapy produced by Kite Pharma (recently acquired by Gilead), has a list price of $373,000. These list prices are only a portion of the total cost of treatment, which can easily exceed $750,000. As a result, cost reduction is a key interest across the industry.

With regard to reagent availability risk, emerging industries typically have emerging supplier bases, which may have only a single supplier for a key good or service. As a result, a shutdown of a major supplier can be highly disruptive. One such disruption, which resulted from sterility issues, recently caused the unavailability of a key cell therapy reagent, bringing therapy production to a halt for 2 months for some manufacturers. In one of our 'what If' studies, due to the above cost considerations, we reduced the number of bioreactors and reagent inventory in our single facility simulation model to a minimum, producing a lean therapy production facility. We then introduced a 2-month reagent disruption. Once the delivery of reagent was resumed and a backorder surge was experienced, the facility was not able to return to normal operations until the number of bioreactors and the amount of reagent in inventory were increased, which provided the facility with the resilience that it needed but at an added cost. Examples of how increasing the number of suppliers for key reagents and how multi-facility (distributed) manufacturing supply chain networks can mitigate reagent availability risk can be found in [1]. We remark that the short shelf-life of the reagents and the in-house manufacturing of buffers and medias with even shorter shelf-lives exacerbate the impact of a supplier disruption.

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A key question in designing a supply chain network in this industry is whether to have a centralized manufacturing network with a single manufacturing facility or a distributed manufacturing network with multiple, geographically distributed manufacturing facilities. Centralized networks, compared to distributed networks, have less demanding regulatory requirements, greater potential for economies of scale, greater consistency in operations, less total capital expenditure, but slower fulfillment times (which may reduce access for some patients). Further, if goods and/or specimens can be transshipped and manufacturing capacity is easily relocatable (e.g., bioreactors, 3D printers) in the distributed network, then a dynamic form of resilience is possible, reducing total resilience capital expenses and allowing facilities to run lean when possible and be resilient when necessary. Dynamic resilience is an emerging and incompletely understood feature of reconfigurable supply chain networks. Automation can potentially help mitigate the difficulty in ensuring uniformity of operations at multiple facilities, although the fast clock speed of technology innovation in this industry represents a barrier to achieving uniformity of operations. Determining the best network design, which our software can support, is application specific and influenced by regulatory requirements, patient demand, and other factors.

The emerging need to optimize reagent inventory, given the inherently high cost of cell therapies, is extensively discussed in [13], and this need is inextricably linked to demand forecasting. Demand forecasting for a new product is invariably a challenge; this challenge for cell manufacturing therapies is heightened by uncertainties surrounding the future regulatory environment and the fast pace of innovation. Using our software, we are now able to determine the optimal manufacturing capacity level and an optimal reagent replenishment policy, given therapy demand and a patient service level (PSL). We describe therapy demand as the probability distribution over demand and PSL as the probability α, where the probability that one or more patients will have to wait for their therapy production to begin is less than or equal to α (ideally, a small probability). We leave scenario development and the number of scenarios to consider up to the user, where a scenario is the pair (therapy demand, PSL). Our foundational analysis is currently based on a stylized model that considers multiple reagents but does not consider the possibility of supply disruptions. Simulation models can be more granular in order to consider supply chain disruptions for different materials with different suppliers and lead times and to provide a more realistic view of how costs accrue throughout the supply chain.

Another challenge that we anticipate emerging in the near future is the specimen queuing discipline at a cell manufacturing facility. Typically, therapy manufacturing begins in the order that patient specimens arrive at the facility, i.e., the first-in-first-out queuing discipline. However, patients can be in various states of health when their specimens arrive. We are currently investigating the impact of another queuing discipline, the priority queue, where a small number of the sickest patients are given priority with respect to the start of their therapy manufacturing, i.e., go to the front of the line. Initial results indicate that the priority queue can significantly reduce the average mortality rate with an indiscernible impact on the mortality rates of patients who are not considered priority cases. These initial results are based on sparse data, are dependent on the percentage of patients that are given priority status, and hence can only be considered tentative. However, the priority queue shows promise as a way of improving overall patient outcomes.

TRANSLATION INSIGHT

Reducing the cost of resilience of reconfigurable supply chain networks for supply chains with geographically distributed manufacturing capacity, determining the optimal manufacturing capacity level and an optimal reagent

replenishment policy for a single cell manufacturing facility, given a demand forecast and a patient service level, and reducing the average mortality rate by giving priority to the sickest patients with respect to the start of their therapy manufacturing are all intended to improve the societal and commercial value of cell manufacturing and supply chain networks.

REFERENCES

1. Wang K, Liu Y, Li Wang B *et al.* A Multiscale Simulation Framework for the Manufacturing Facility and Supply Chain of Autologous Cell Therapies. *Cytotherapy* 2019; 21(10): 1081–93
2. Clarke L. Building robustness and scalability into the immuno-oncology supply chain. *Cell Gene Ther. Ins.* 2019; 5(5): 925–8.
3. Clarke D, Smith D. Managing starting material stability to maximize manufacturing flexibility and downstream efficiency. *Cell Gene Ther. Ins.* 2019; 5(2): 303–14.
4. Baila S, Frechette M, Francis K, Goel D. Critical needs and challenges for the cell and gene therapy raw materials supply chain. *Cell Gene Ther. Ins.* 2019; 5(9): 1425–30.
5. Wartel C, Villavicencio U. Identifying and mitigating risks in the viral vector supply chain. *Cell Gene Ther. Ins.* 2019; 5(10): 1339–46.
6. Roy K. Identifying Critical Quality Attributes of cellular starting materials. *Cell Gene Ther. Ins.* 2019; 5(2): 275–21.
7. Hostetler A, Maybach G. Mitigating raw materials risk during preclinical-clinical transitioning. *Cell Gene Ther. Ins.* 2019; 5(9): 1377–84.
8. McFarland R, Kljavin I, Moore T. Tackling the critical issues pertaining to raw & starting materials for cell & gene therapy manufacturing. *Cell Gene Ther. Ins.* 2019; 5(2), 259–63.
9. Tischner C. Building flexibility into GMP CAR T cell therapy manufacture. *Cell Gene Ther. Ins.* 2019; 5(10): 1385–90.
10. Szczur K. Challenges in viral vector raw materials procurement & management. *Cell Gene Ther. Ins.* 2019; 5(10): 1305–10.
11. Wilfong C, Lowther D. Keys to successful supply chain data management for T-cell immunotherapy. *Cell Gene Ther. Ins.* 2019; 5(Suppl. 7): 699–704.
12. Croteau J. Supply chain data management and integration: process development and manufacturing. *Cell Gene Ther. Ins.* 2019; 5(S7): 999–1003.
13. Presher C. Mitigating risk in the gene therapy supply chain. *Cell Gene Ther. Ins.* 2019; 5(9): 1069–73.
14. De Naeyer D. Preparing a patient-specific cellular immunotherapy supply chain for commercialization. *Cell Gene Ther. Ins.* 2019; 5(9): 1117–23.
15. Curtis M, Philipson R. Cell & Gene Therapy Commercial Insight – October 2019. *Cell Gene Ther. Ins.* 2019; 5(11): 1573–90.
16. Wilson A, Cockroft A. Regulatory considerations for decentralized manufacture of ATMPs. *Cell Gene Ther. Ins.* 2019; 5(10): 1213–24.
17. Ghosh A, Gheorghe D, DRG Oncology, CAR T-Cell Therapies: Current Limitations & Future Opportunities. *Cell Gene Ther. Ins.* 2019; 5(5): 9–19
18. Imbach KJ, Patel A, Levine AD. Ethical considerations in the translation of CAR-T cell therapies. *Cell Gene Ther. Ins.* 2018; 4(4): 295–307.

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