Proceedings of the 2022 Winter Simulation Conference
B. Feng, G. Pedrielli, Y. Peng, S. Shashaani, E. Song, C.G. Corlu, L.H. Lee, E.P. Chew, T. Roeder, and P. Lendermann, eds.

THE IMPACT OF BATCH DISPATCHING ON VACCINE MANUFACTURING THROUGHPUT

Robin Kelchtermans
Donovan Guttieres
Carla Van Riet
Catherine Decouttere
Nico Vandaele

Department of Decision Sciences and Information Management
KU Leuven
Naamsestraat 69
Leuven, 3000, BELGIUM

ABSTRACT

The COVID-19 pandemic has highlighted the challenge of rapid, large-scale vaccine production following an unanticipated spike in demand. Increasing the total throughput of a vaccine manufacturing network is crucial. However, the production process is complex and has many distinct steps, each with high stochasticity. Discrete event simulation is used to simulate this manufacturing network, with a focus on testing the impact of dispatching rules used to allocate batches between drug substance and drug product sites. We propose a new dispatching rule based on a push-pull mode, often observed in practice. This increases the utilization of the network and keeps the batches at the drug substance site for a longer period, which improves flexibility in the allocation.

1 INTRODUCTION

Vaccines against SARS-CoV-2 have been developed and brought to market at an unprecedented speed and have led to an estimated 14.4 million fewer deaths due to COVID-19 within the first year of their introduction (Watson et al. 2022). During a pandemic, increasing manufacturing throughput and vaccine access is crucial to reach population-wide immunity as fast as possible.

The traditional vaccine manufacturing process is characterized by long lead times, high setup costs and process uncertainties. The production yields may vary due to the biological nature of the process. Production lines or entire sites must be shut down for weeks if a bacterial contamination happens. Furthermore, high quality assurance and quality control standards make the process challenging, lengthy and costly.

A vaccine manufacturing network typically compromises of drug substance (DS) and drug product (DP) sites. Several technology platforms (e.g., mRNA, viral vector) exist for the manufacturing of the DS, but this research focuses on settings with large bioreactors in which cells are grown and antigens are subsequently harvested. Bulk batches are shipped to a DP site, where they are formulated to make the vaccine more stable and immunogenic, filled into vials or syringes and packed for distribution.

The vaccine manufacturing network (Figure 1) can consist of multiple DS and DP sites. Sites can have different capacities and number of parallel processes (i.e. number of bioreactors, formulation vessels, filling and packaging lines). Often a static dispatching rule is used to allocate batches between DS and DP sites. Regulatory requirements have a significant impact on the network structure (e.g., restrictions on transferring a batch from one DP to another).

Although there are multiple ways to increase throughput (e.g., increase capacity of sites by adding lines, building new sites, reducing process time), these are considered resource- and time-intensive. This

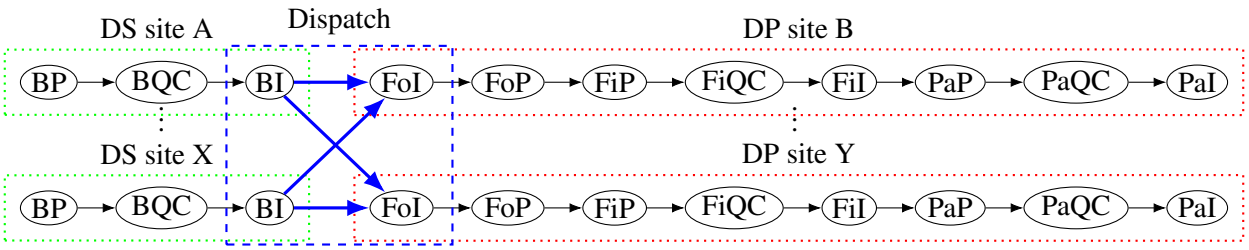

Figure 1: Vaccine manufacturing network with two or more drug substance (DS) and drug product (DP) sites. With B=bulk, P=process, QC=quality control, I=inventory, Fo=formulation, Fi=filling, Pa=packaging.

work focuses on increasing utilization of an existing network in the early stages of an outbreak to address supply scarcity, specifically, by improving the allocation of batches between DS and DP sites.

Based on first simulation experiments conducted using Julia – a novel high-level, high-performance, dynamic programming language (Bezanson et al. 2017) –, the network throughput is highly sensitive to the way batches are allocated from DS to DP sites. The aim is to close supply gaps by improving batch allocation across sites in order to reduce the manufacturing lead time.

2 METHOD

Based on the simulation approach proposed by Lostumbo et al. (2021) and given the stochastic nature of a vaccine manufacturing network, discrete-event simulation is used to model each process time as a probability distribution, validated by experts during stakeholder interviews. We model the entire manufacturing network of a vaccine with both multiple DS and DP sites (Figure 1). We use a situationally aware dynamic approach to dispatching, since it takes the current instant state of the simulation and unexpected events into account (Chan et al. 2020). We do this by minimizing equipment idle time (i.e., increasing utilization) of all process at the DP sites and by keeping the batches as long as possible at the DS sites. This allows more flexibility for the dispatching of the batches, since it can react to sudden changes of the network (e.g., contaminations). We compare this to three less complicated dispatching rules, namely a random allocation, a sequential allocation and a rule that assigns the batch to the DP with the lowest stock.

3 RESULTS & DISCUSSION

The preliminary results show differences across the allocation rules. The variation in throughput remains high, irrespective of the dispatching rule applied. Therefore, we are currently developing dispatching rules that include regulatory constraints, as we hypothesize that allowing the transfer of batches from one DP site to another could increase the overall throughput, and reduce potential future uncertainties. Furthermore, we analyze the effects of the network configuration of DS and DP sites on the throughput.

REFERENCES

Bezanson, J., A. Edelman, S. Karpinski, and V. B. Shah. 2017. "Julia: A Fresh Approach to Numerical Computing". *SIAM review* 59(1):65–98.

Chan, C. W., B. Ping Gan, and W. Cai. 2020. "Towards Situation Aware Dispatching in a Dynamic and Complex Manufacturing Environment". In *Proceedings of the 2020 Winter Simulation Conference*, edited by K.-H. Bae, B. Feng, S. Kim, S. Lazarova-Molnar, Z. Zheng, T. Roeder, and R. Thiesing, 528–539. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.

Lostumbo, M. A., M. Saiz, A. A. Juan, D. Lopez-Lopez, and L. Calvet. 2021. "Combining Simulation with Reliability Analysis in Supply Chain Project Management Under Uncertainty: a Case Study in Healthcare". In *Proceedings of the 2021 Winter Simulation Conference*, edited by S. Kim, B. Feng, K. Smith, S. Masoud, Z. Zheng, C. Szabo, and M. Loper, 1–11. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.

Watson, O. J., G. Barnsley, J. Toor, A. B. Hogan, P. Winskill, and A. C. Ghani. 2022. "Global Impact of the First Year of COVID-19 Vaccination: a Mathematical Modelling Study". *The Lancet Infectious Diseases* 22(9):1293–1302.