Merck Animal Health Uses Operations Research Methods to Transform Biomanufacturing Productivity for Lifesaving Medicines

Citation for published version (APA):

DOI:
10.1287/inte.2022.1147

Document status and date:
Published: 31/01/2023

Document Version:
Accepted manuscript including changes made at the peer-review stage

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Download date: 19. Mar. 2024
Merck Animal Health Uses Operations Research Methods to Transform Biomanufacturing Productivity for Lifesaving Medicines

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Abstract

Merck Animal Health offers veterinarians, farmers, pet owners, and governments a wide range of veterinary pharmaceuticals, vaccines, health management solutions and services, and an extensive suite of connected technology that includes identification, traceability, and monitoring products. Biomanufacturing uses living organisms (i.e., viruses and bacteria) to grow the active ingredients in vaccines, pharmaceuticals, and therapeutics. This high-tech manufacturing process generates unique challenges not found in many other industries. For example, biomanufacturing operations include high levels of uncertainty and batch-to-batch variability in production yield, lead times, and costs. Additionally, the high cost of equipment and labor-intensive nature of operations preclude the ability to flexibly add capacity. Facing these challenges, we decided that harnessing the power of operations research and advanced
analytics to complement our rich life sciences and biomanufacturing expertise was critical. After four years of collaboration with the Eindhoven University of Technology, we developed a portfolio of optimization models and decision support applications, which substantially improved our biomanufacturing effectiveness. The implementation of the developed models had a significant impact by generating $200 million of additional revenue, without the need for additional raw materials, energy resources, or new equipment. The developed models are widely adopted across the firm, thus enhancing its core function.

Keywords: biomanufacturing • life sciences • simulation • data analytics • stochastic modeling • Edelman award
Introduction

Merck Animal Health produces lifesaving medicines for companion and food-producing animals. The company’s official name is Merck Animal Health in the United States and Canada, and MSD Animal Health elsewhere; we use Merck Animal Health in the remainder of this paper. The use of veterinary medicines also benefits humans by reducing the spread of disease between animals and humans, and facilitating a safe, efficient, and sustainable food supply. We produce various types of medicines, including vaccines to protect against diseases, pharmaceuticals (e.g., antibiotics) to treat diseases, and therapeutics (e.g., insulin) to improve body functions and provide benefits for a range of conditions. Our customers have always known that they can depend on us not only for medicines but also for information, technologies, and veterinary services that advance healthcare. Our facility in Boxmeer, Netherlands is the largest biomanufacturing hub of Europe for veterinary medicines, and the second largest in the world. In this facility, we conduct both large-scale manufacturing of more than 60 active ingredients, and the research and development of new medicines.

The modern use of biomanufacturing started in the 1970s with genetically engineered E. coli to synthesize human insulin. Since then, the research and development (R&D) of new biopharmaceuticals has exploded. More than 8,000 medicines are currently in global R&D pipelines to treat cancer, neurologic disorders, and many other diseases (International Federation of Pharmaceutical Manufacturers and Associations 2021). In the animal health industry, these drugs serve over 640 million food animals and 383 million companion animals in the United States alone (The Animal Health Institute 2020).

To date, the competitive advantage in biomanufacturing to produce medicines has been primarily driven by science (i.e., the scientific knowledge related to the underlying biological and chemical processes and the methods used to harness these to produce active ingredients). The industry started with chemical firms who set up labs to discover and produce medicines.
With growing market demand and competition, there is currently an increasing need for making biomanufacturing operations “smarter” to reduce costs, decrease lead times, and improve the production yields of these critical medicines.

**Project Background**

We start with providing background information on biomanufacturing. First, we elaborate on the characteristics of biopharmaceutical drugs, and discuss the basics of biomanufacturing operations. Next, we reflect on the challenges associated with the fermentation processes and the end-to-end planning activities. Finally, we overview our solution approach.

**Complexity of Biopharmaceutical Drugs**

Biopharmaceutical drugs are fundamentally different from conventional drugs. In conventional pharmaceutical manufacturing, the drugs (e.g., small molecule drugs such as aspirin) are chemically synthesized. For example, aspirin is prepared by chemical synthesis from salicylic acid, through acetylation with acetic anhydride. Some drugs (e.g., antibiotics) involve microbiology and the growth of molds and yeast to produce valuable compounds (Demain and Martens 2017). In contrast, biomanufacturing uses living organisms (e.g., bacteria, cell lines, and/or viruses) that serve as a source for biochemical activities in making the desired active ingredients. A recent example is the underlying technology of COVID-19 vaccines. The immune system responds to the spike protein of the SARS-COV-2 virus, creating a specific response in fighting the viral infection. The mRNA vaccine technology uses the cells’ native protein synthesis to create the proteins that can invoke the same immune response. In summary, the resulting active ingredients in biomanufacturing are typically proteins, antibodies, and antigens.
Figure 1. Biopharmaceutical Drug Molecules Are More Complex in Shape, Size, and Structure Compared with Conventional Drug Molecules

Living organisms are used in the production process, thus enabling the production of active ingredients that are highly sophisticated and complex. Figure 1 illustrates a biopharmaceutical drug molecule and a conventional drug molecule to contrast their size, shape, and structure. This complex structure of the biopharmaceutical drug molecule helps active ingredients to have “smarter” capabilities. For example, these smart molecules can carry special messages for the immune system or search for a tumor in the body and bind to it (instead of damaging healthy cells). Because of their advanced structure and capabilities, these medicines are referred to as “next-generation drugs.” However, the use of living organisms in production leads to challenges that many other industries do not experience. These include high levels of uncertainty (often a direct function of limitations in scientific knowledge that impact production) and batch-to-batch variability in production yield, lead times, and costs at all stages of the biomanufacturing processes.

Basics of Biomanufacturing for Medicines

Biomanufacturing processes can be categorized into two main production steps (see Figure 2): (1) Upstream processing (USP) where organisms are cultivated and active ingredients are produced using modern fermentation processes. Examples of support steps or processes include
preparation of the medium and seed cells, cleaning, monitoring the bioreactor, bioreactor transfers, and quality control.

(2) Downstream processing (DSP) where the solution obtained from the upstream process goes through several purification steps (e.g., centrifugation, chromatography, filtration) to achieve the desired requirements on product safety and quality. Support steps or processes include various levels of cleaning, measurement, and the creation of media and reagents.

**Figure 2.** The Production Process Can Be Categorized into Two Steps, USP and DSP

![Diagram](https://via.placeholder.com/150)

From the first step in USP until the last operation in DSP, the manufacturing process for a single medicine contains around 4,000 to 8,000 different production steps in our daily operations at Boxmeer. These production steps mostly include the preparation of media and cells, cleaning and sterilization of equipment, upstream bioreactor processes, purification processes, inspection, and documentation. Most of these production steps are done to ensure the process sterility and purity of active ingredients. We next elaborate on the challenges in biomanufacturing operations and end-to-end scheduling activities.

**Complexity and Challenges of Modern Fermentation Processes**

The first step in biomanufacturing is to “grow” the desired end products through a modern fermentation process. We use the term “modern fermentation” to refer to the fermentation of biopharmaceuticals, whereas “classical fermentation” denotes the fermentation in the process industry (e.g., wine or yogurt making). The modern fermentation process is carried out in a stainless steel vessel called a bioreactor (see Figure 3 for an example). The bioreactor process starts with a seed culture and a medium specifically designed to support the cell growth. The seed culture typically consists of bacteria and serves as a source for making the desired active ingredients. The bioreactor is equipped with sensors that enable real-time monitoring and
control. Once the bioreactor process starts, the seed culture grows (referred to as cellular multiplication) and produces the desired active ingredients via modern fermentation. Microbial growth advances through four typical phases, as Figure 3 illustrates. Of these phases, the exponential growth phase is the most important, because the number of cells and desired end products (i.e., active ingredients) increase exponentially inside the bioreactor. When this growth stops, the stationary phase is entered. The goal is to harvest the active ingredients as soon as the process enters the stationary phase. The output of the bioreactor is a batch solution consisting of the desired active ingredients along with several unwanted metabolic wastes such as dead cells. In some cases, the cell culture is grown through a progressively larger series of bioreactors (so-called bioreactor operational chains). Subsequently, the batch continues with several downstream purification steps to achieve the desired quality requirements for the end product.

**Figure 3.** Bioreactors Provide a Controlled Environment to Support Cell Growth (Left); the Cells Inside the Bioreactor Follow Various Growth Phases to Produce the Active Ingredients (Right).

The bioreactor processes are stringently regulated, so that we follow a “recipe” that prespecifies operating ranges for critical process parameters (e.g., temperature, pH, oxygen flow). Although we replicate entirely identical process configurations for each batch, as prescribed in the recipe, we deal with uncertainty and batch-to-batch variability in the bioreactor outcomes. For example, we often encounter uncertainty in the batch yield, quality, and the
duration of the cell growth phases. Figure 4 shows the batch-to-batch variability in bioreactor yields based on our production data. In this figure, we plot the yield (i.e., amount of active ingredients) of 21 batches. Although all these batches were operated under identical configurations (i.e., using the same equipment and recipe), they resulted in different production yields. The batch-to-batch variability and process uncertainty is a common challenge in the industry. One of the major causes of this uncertainty is the use of living organisms in biomanufacturing. Other factors, such as limitations in scientific knowledge and variability in starting materials (e.g., seed culture, media) also contribute to the uncertainty in bioreactor outcomes.

Figure 4. To Illustrate Batch-to-Batch Variability, We Plot the Bioreactor Yield Obtained from 21 Batches that Were Operated Under Identical Configurations

Bioreactor setup is another critical challenge in the industry. The bioreactor needs to be cleaned and sterilized after each use. These setup activities also include preparation of the seed culture and media, and setup of other necessary equipment such as sensors. In practice, bioreactor setups require highly specialized labor and materials, and are known to be costly and time consuming. For example, setup activities may constitute up to 25% of bioreactor processing times and costs in our setting. The high cost of setups motivates the industry to obtain as much yield as possible from each batch.
End-to-End Planning and Scheduling Complexity

We now elaborate on the scale and complexity of our manufacturing operations in more detail. In our Boxmeer facility, our manufacturing system consists of 8,000 interdependent process steps each day to produce 60 active ingredients critical to a range of medicines. This work is split across multiple semi-autonomous process lines (PL), where each PL has a similar flow, but the sequence and cycle time of the steps vary between “recipes,” even for the same product. A recipe in this context describes the manufacturing steps from starting material to final active ingredient through one particular production path.

Complexity in our production environment is driven not only by the considerable number of steps but also by several critical manufacturing characteristics and their interdependencies.

1. Alternative production paths: The same product can be produced with different recipes or alternative production paths. For example, one bioreactor might handle twice the volume of another. As another example, we have diverse types of filtration available—one recipe may accept filtration 1 or 2, while another recipe only accepts filtration 3. Some products have preferred paths.

2. Alternative resources: Alternative sets of equipment can be utilized for a production step; however, they do not necessarily have identical performance characteristics. Another critical constraint is the skill set of the operators who oversee the equipment.

3. Continuous flow process (zero wait-time constraint): There are only a few steps in the manufacturing process where the work-in-progress (WIP) can be stored to wait for a resource (e.g., equipment) to become available for the subsequent step. This is referred to as the zero wait-time constraint. Where there is a wait place, that additional time can impact the batch yield and quality.
4. Coordination of multiple activities for process execution: Multiple distinct activities must take place before a manufacturing step can start, and we need to coordinate them properly. For example, to start a modern fermentation process, we need to clean and sterilize the bioreactor, prepare the media and the cell culture, and calibrate the sensors. Only then can the modern fermentation process start.

5. Cycle time variability: The processing times (e.g., fermentation time) on a resource (e.g., bioreactor) varies considerably from product to product.

6. Parallel starts: Because each PL has multiple bioreactors, the production process of multiple products can start simultaneously.

7. Pipeline process: Once a manufacturing activity (e.g., fermentation) has completed, the solution is passed downstream, the resource is reset for readiness, and that resource is then used for another manufacturing activity. In this setting, we need to carefully plan the start time of a job on each equipment. Otherwise, the jobs may compete for the same downstream resource if the scheduling decisions do not consider the subsequent steps.

Figure 5 (color online). There Is a Complex Interaction Between Batch Sizing, Resource Allocation, and Scheduling Decisions

Notes. We present an illustrative example with five products (P1-P5), three possibilities for batch size (A, B, C), and three process lines (PL1-PL3). Each PL contains a different bioreactor type. Different colors denote different products. The Gantt chart in the bottom shows the start
times and the production sequence on each PL. For example, process line PL1 starts with product P1 using batch size A (P1_A) and continues with product P2 using batch size A (P2_A). Light color between P1_A and P2_A denotes setup.

Moreover, there is a complex interaction between batch sizing, resource allocation, and scheduling decisions. Consider the example in Figure 5. In this example, there is a requirement to produce five products (P) in a given period for USP. In this setting, we need to decide (1) the batch sizes to meet the production requirements, (2) the allocation of products to process lines, and (3) the production sequence (e.g., the start time of a product on a PL). Figure 5 shows three potential batch sizes (A, B, C) for each product. For example, P1’s production requirement will be met with two batches (A and B) on process line PL1, while P2 will be produced with one batch of size A on PL1 and two batches of size B and C on PL2. The last layer in the figure (sequence timing) shows the production sequence on each PL. As Figure 5 illustrates, there are many feasible options for the allocation of products to process lines, and the sequencing of products for a given process line. However, equipment is limited, and we have a zero-wait time constraint. Hence, there is ample opportunity for a collision (i.e., two recipes needing the same piece of equipment at the same time). Given the zero wait-time constraint, a collision then directly results in yield loss. In this highly connected setting, a good production planning and scheduling system is critical to avoid infeasible schedules (collisions) and gaps of idle capacity.

**Solution Overview**

We started the project with a clear vision of *improving the output of our production facility at Boxmeer without increasing capacity*. Our primary objective was to make a transformation towards “smart operations” by proactively using data analytics and operations research (OR) in our daily decisions.

In conjunction with experts from the School of Industrial Engineering at Eindhoven University of Technology in the Netherlands, we identified two primary opportunities to
achieve our vision, as we illustrate in Figure 6. We will next describe the details of our project and the solutions we developed.

**Figure 6.** We Had Two Primary Objectives: (1) Improving Bioreactor Yield, and (2) Improving End-to-End Planning and Scheduling

### Project 1. Improving Bioreactor Yield

To support our objective to improve bioreactor yield, we conducted two (independent) optimization projects: (1) implementation of a novel technology called “bleed-feed” to reduce bioreactor setups; and (2) optimization of bioreactor settings for selected products, as illustrated in Figure 6. We now elaborate on these two projects. We start with the bleed-feed optimization project, and then discuss the bioreactor optimization project.

#### Project 1.a. Bleed-Feed Optimization

The bioreactor must be cleaned and sterilized after each use. These setup activities require resources, such as buffers, mediums, reagents, and special equipment. The bioreactor setup is also time consuming and expensive because it can constitute up to 25% of fermentation processing lead time and cost. Therefore, there is a significant business case in the industry to reduce the number of bioreactor setups.

To achieve this, we adopted a new technique called *bleed-feed*. Bleed-feed is also a relatively new technique in the life sciences literature. With this technique, instead of harvesting the entire batch at the stationary phase, some fraction of the cell culture is extracted during the exponential growth phase (“bleed”) and a special medium is added (“feed”). Subsequently, the
remaining cell culture acts as a seed for a new bioreactor run and continues to grow at the exponential growth phase. Therefore, the bleed-feed technology prolongs the duration of the exponential growth phase, and also helps to allow skipping the setup of the subsequent batch. Hence, the bleed-feed technique provides a significant opportunity to reduce bioreactor costs and lead times.

The challenge is that the bleed-feed process can only be performed in the exponential growth phase. In this setting, identifying the best bleed-feed time is challenging because the time at which the exponential growth phase stops is unknown beforehand (i.e., the duration of each cell growth phase is stochastic). This implies that if we carry out the bleed-feed process too early, we will not obtain the maximum yield from that batch. If we run it too late, cells are in the stationary phase; therefore, we have to harvest (stop) the entire batch and incur the penalty of setting up another batch. We illustrate the tension between the probability of entering the stationary phase and the bioreactor yield in Figure 7. Observe from Figure 7 that both the probability of entering the stationary phase and the bioreactor yield are increasing over fermentation processing time. Hence, there is a clear trade-off between improving the bioreactor yield and increasing the failure risk by delaying the bleed-feed time (Koca 2022).

**Figure 7.** This Plot Shows how the Probability of Entering the Stationary Phase and the Bioreactor Yield (per Setup) Change as a Function of the Fermentation Processing Time

![Figure 7](image)

*Note.* The original data are scaled and the axes are removed to protect confidentiality.
To address this trade-off and identify an optimal bleed-feed time, we developed an optimization model that maximizes the expected yield obtained per bioreactor setup. We built the optimization model based on the Markov decision process (MDP) theory and calibrated it with real-world data. The MDP model combines cell-level dynamics (i.e., cell growth phases and yield accumulation mechanisms) with manufacturing-level dynamics (i.e., the trade-off between performing the bleed-feed too soon versus too late) to support decision making.

The input to the model relates to the underlying dynamics of the modern fermentation process, such as the initial number of seed cells, biomass accumulation rate, and parameters of the probability distributions associated with the duration of the cell growth phases. The fermentation process is monitored at discrete time intervals, called decision epochs. In practice, these decision epochs could be every minute, hour, or day depending on the specific application and end use. The state space of the MDP model represents the key parameters for decision making. In our problem setting, there are three critical components of the state space: First, we monitor the age of fermentation. This state represents the time elapsed from the last bioreactor setup or bleed-feed operation. Second, we capture the growth rate of the cell culture. Third, we record the number of bleed-feed operations performed so far to comply with regulatory limitations.

At each decision epoch, we have two actions: we can either continue the fermentation over the next decision epoch or perform the bleed-feed. If we bleed-feed, the age of fermentation resets, we have uncertainty in the growth rate of the subsequent batch, and the bleed-feed count increases by one. Ultimately, this is an optimal stopping problem. To mimic the biological dynamics of modern fermentation processes, we established the state transitions of the MDP model based on Monod-type equations obtained from the life sciences literature (Monod 1949, Doran 1995). The objective of the MDP model is to maximize the expected biomass production per setup.
As an output, the model reports the optimal time to perform the bleed-feed operation based on the actual status of fermentation (i.e., the amount of active ingredients accumulated inside the bioreactor, the growth rate of the cells, and the number of bleed-feed operations performed). We also analyzed the mathematical properties of optimal bleed-feed policies and showed that they have a control-limit structure (i.e., it is optimal to bleed-feed when the age of fermentation is greater than a specific value). We refer the reader to Koca et al. (2022) for details on the optimal bleed-feed policies and analytical results.

**Project 1.b Bioreactor Optimization**

Once a bioreactor has been set up, a natural incentive is to achieve the highest possible yield from that batch. The fermentation “recipe” prespecifies a feasible range for the critical process parameters (e.g., the temperature inside the bioreactor should be between X and Y Celsius degrees). Within these feasible ranges, it is possible to identify an “optimal” process configuration to maximize the batch yield. However, finding the best configuration for the critical process parameter was a challenging problem in our setting (we do not disclose the name of the critical process parameter for confidentiality). No existing work was available in the literature to estimate how production yield of our specific cell culture would change as a function of the critical process parameter. Therefore, we needed to conduct several experiments to understand this relationship. However, conducting these experiments at a small scale was not possible because of resource limitations and potential scalability issues. This implied that experiments needed to be conducted at an industry-scale bioreactor (comparable with industry standards). Subsequently, this led to an optimal learning problem, where the relationship between the critical process parameter and yield needed to be quantified under a limited number of industry-scale experiments. Note that these experiments were expensive because they were conducted on actual production orders (within prespecified regulatory ranges). Therefore, we
needed a smart experimental design mechanism to identify the best parameter configuration at
a limited number of experiments.

Our main problem was to smartly design an information collection policy in such a way
that it would eventually lead us to the optimal value of this critical process parameter. To
address this problem, we adopted a Bayesian approach and modeled the uncertainty in the yield
function by using a Gaussian process prior, which is commonly used to model continuous
functions in Bayesian spatial statistics (Powell 2010, Frazier 2018). We determined the value
of the starting Gaussian process prior based on expert opinion and domain knowledge. Then,
we built a dynamic programming (DP) model with the objective of finding the best information
collection policy that would maximize the expected yield. Following the literature on Bayesian
methods for simulation optimization, we used the knowledge-gradient (KG) policy to build a
one-step ahead approximation to the optimal policy (Powell 2010, Frazier 2018). Based on this
information, the KG policy suggests a specific value to be tested in such a way that the expected
difference in the values between our current knowledge on the prior distribution and our one-
step look-ahead knowledge on prior distribution is maximized. We refer the reader to Martagan
et al. (2021) and Koca (2022) for details on the mathematical model and solution approach.

Figure 8. The Graph Illustrates how the Batch Yield Changes as a Function of the Critical
Process Parameter

Notes. The original curve is scaled to protect confidentiality. The challenge is to estimate this
functional relationship based on a limited number of experiments under process uncertainty.
The output of the bioreactor optimization tool is an information collection policy and an estimate of the best value of the critical process parameter that maximizes the expected yield. Figure 8 illustrates the output of the tool. This figure presents the expected yield as a function of the critical process parameter. In this example, we conducted eight real-world experiments to build this function. The tool provided a formal and rigorous approach for optimally designing experiments to support bioreactor process improvement projects.

**Project 2. Improving End-to-End Planning and Scheduling**

We started to rethink our planning and scheduling activities in 2017. Initially, our objective was to use historical data to build process maps (e.g., value-stream maps) to achieve a better understanding of our manufacturing lead times. However, this would only show us what happened in the past and be of limited help in supporting our current planning and scheduling decisions (e.g., which product to start on which process line, when to start it, and which recipe to use). Thus, the aim and scope of the project quickly transitioned to developing a planning and scheduling optimization model.

The project proceeded in three phases: (1) Collection of process data; (2) discrete-event simulation modeling to support what-if analyses to test various alternatives from different production plans to capacity enhancements; and (3) optimization to search through alternatives to find those that best meet business objectives.

In the first phase, we systematically collected and organized all the relevant data for each of the 8,000 production steps in our Boxmeer facility. This data include details such as bioreactor processing times, which products can use which bioreactor, batch quality, yield, and much more. The data collection process was not straightforward. Although we routinely collected process data for regulatory purposes, we needed different metrics for production planning and scheduling decisions. In some cases, we had to manually extract data from equipment, or use optical character recognition software to digitize handwritten paperwork and
lab notes. Hence, Phase 1 was our first attempt to systematically collect and analyze all the data related to our 8,000 production steps.

In the second phase, we built a discrete-event simulation model using the data from Phase 1 to support capacity planning decisions through what-if analyses. Using the simulation model gave us a better understanding of our production capacities, lead times, and costs. For example, we evaluated the impact of various capacity planning decisions (i.e., batch sizing, resource allocation, equipment selection) on the expected throughput and lead times. The simulation model helped us realize that we could increase our throughput by simply making better-informed scheduling decisions without expanding our capacity.

In the third phase, we expanded the scope towards optimization. Figure 9 provides a high-level sketch of our planning and scheduling optimization framework (we omit the details for confidentiality). Our main objective is to minimize the makespan (i.e., the time elapsed from the start of the first operation in USP until the end of the last operation in DSP). For this purpose, the optimization model considers several practically relevant constraints, as summarized in Figure 9. For example, we account for equipment and personnel availability. Sometimes, equipment is taken out of service for preventative maintenance. Each operator’s daily availability is influenced by his/her shift schedule, flexible break times, skillset, and nonproduction-related activities. We also have staffing goals, such as minimizing weekend work, accommodating cross-training, and task switching between operators. Again, a “recipe” in this context specifies all the manufacturing steps from starting material to final active ingredient. The output of the optimization model consists of decisions related to resource allocation (i.e., which products are produced on which process lines), batch sizing (i.e., how much to produce to meet the production requirements), and the scheduling of each process line (i.e., when to start a specific job using a specific machine at a given process line).
Prior to developing the optimization model, we did not have a systematic approach for using real-world data to support our planning and scheduling decisions. Our planning and scheduling took place manually in an Excel sheet. This was both time consuming and prone to error and lacked the sophistication we required to manage our production processes. Even commercially available scheduling software designed for pharmaceutical manufacturing could not satisfy our ambition to maximize our production efficiency (because schedule improvements were still a manual what-if exercise). Therefore, we built our own solution to capture the complex dynamics of our production processes.

**Innovative Synthesis of Life Sciences with Operations Research**

Kinetic models in life science describe the biological and chemical dynamics of fermentation processes (e.g., Almquist et al. 2014). For example, these models can describe the cell growth rate and the impact of nutrients on cell growth during fermentation. However, kinetic models are not adequate to support our business and production decisions (especially under uncertainty in the core manufacturing processes). An innovative synthesis of life sciences with operations
research methodologies was critical to increase biomanufacturing effectiveness, as illustrated in Figure 10.

**Figure 10. Closing the Loop: Operations Research Complements Life Sciences in Our Project**

Compared with other industries such as automotive and semiconductor manufacturing, the application of OR is relatively new to the biomanufacturing industry, perhaps due to the initial challenge of basic mastery of the core technology. There are only a few documented accounts of success and a limited number of research papers on biomanufacturing in the OR literature (Martagan 2018, Koca 2022). As more biomanufacturers embrace OR, we believe that this will significantly help the industry provide faster and more affordable access to critical medicines.

**Impact**

We started with the end-to-end planning and scheduling project in 2017, followed by the yield optimization model in 2018, and the bleed-feed optimization in 2020. The models, which we implemented in our daily operations, generated significant impact, as we list below.

- By optimizing the bleed-feed process alone, we achieved an approximately 82.5% higher yield per bioreactor setup.
• By optimizing the critical process parameter of fermentation, we realized an improvement in batch yield of approximately 50% to 60%. Standardizing these parameters reduced our batch yield variability (i.e., standard deviations) by 20%.

• By optimizing our end-to-end planning and scheduling activities, we were able to produce one extra batch per week per production line across multiple production lines.

In total, we generated around $200 million worth of revenue, with more to come, without requiring additional raw materials, energy resources, new equipment, or facility space. We estimated the financial benefits based on a cost-of-goods analysis; see Xu et al. (2020) for an example. We omit the details for confidentiality purposes. Merck Animal Health is a $4.7 billion business globally; thus, the additional revenue from our Boxmeer facility is equivalent to 4.25% of our global revenue.

Moreover, we realized the following additional benefits:

• Environmental footprint: We now require 40% less energy to produce the same volume of product, saving 240,000 cubic meters of gas and 1,200,000 kilowatt hours of electricity and reducing our carbon emissions by 468 tons and our environmental footprint, accordingly.

• Transformation of culture: Prior to this project, operational decisions were primarily made based on domain expertise. With the implementation of the project, however, data analytics and OR started to have a more prominent role in our daily decisions. We established a new OR team to support this more prominent role within our organization.

• Creation of new positions to support analytics: We created 10 new positions for industrial engineering master’s students, most of whom have continued as full-time employees.

• Better response to market needs: The animal health industry at large cannot currently produce enough supply to meet market demand worldwide. Each additional unit
produced is important in delivering our lifesaving medicines and making them more accessible and affordable to patients and animals around the world. In addition to increased flexibility in manufacturing and scheduling, the increase in the production output enabled us to delay a planned capital investment to meet rising demand. Moreover, reducing the need for rework and the improved reliability of finished products facilitated our ability to better match market demand.

**Transportability and Future Work**

With successful test runs, one of our plants in the United States is currently implementing bleed-feed at one of its process lines. Hence, our project has already demonstrated the transportability of our solutions. We are also setting up implementation initiatives at our other facilities in the United States and Europe. Moreover, we are exploring the opportunities for expanding our scope to the human health department within Merck.

Currently, we are establishing a four-year research agenda in collaboration with Eindhoven University of Technology. In the short term, our ambition is to build more advanced prediction models to make real-time inferences on the bioreactor output. With the development of such prediction models, we believe that we can eliminate several costly and time-consuming inspection activities, and further increase our production yields. Moreover, we aim to develop new optimization models tailored for the specific needs of continuous biomanufacturing processes (Subramanian 2017). Although the developed models have been a first step towards bioprocess optimization, there is significant potential for exploring the use of data analytics and OR to support continuous biomanufacturing applications.

At Merck, we believe in One Health—an integrated approach to the health of humans, animals, and the environments in which we live. By combining advanced analytics and OR to improve biomanufacturing efficiency, our work influences all three aspects of the One Health concept:
• When we are able to produce more products without using more resources, we lower our carbon footprint.

• More products mean increased accessibility of lifesaving medicines for healthier animals.

• Healthier animals mean a more sustainable food supply, protection against zoonotic diseases (i.e., diseases transmitted from animals to humans), a reduction in certain food-borne diseases, and longer and happier companionship for pets and their owners.

We would like to also emphasize that One Health is not limited to Merck. The United Nations recognizes One Health and has called for the adoption of integrated human, animal, and environmental health expertise and policy (World Health Organization 2022). By adopting an OR-driven approach, we will continue serving towards our One Health ambition, and thereby improving the health and well-being of animals, humans, and the environment.

Conclusions

To improve biomanufacturing effectiveness, we developed a portfolio of optimization models and decision support applications. The project aligns with our motto “Invent. Impact. Inspire.” By combining knowledge from life sciences and OR, we built a variety of new optimization models for biomanufacturing (Invent). We achieved a significant impact with increased production yields without expanding our capacity (Impact). The results inspired several follow-up projects within Merck, both nationally and internationally (Inspire).

We believe we have an ethical responsibility to continuously improve and share these methods and our expertise with our global community. Through the work we have presented, we have proven that linking OR with life sciences in biomanufacturing drives substantial, sustainable, and scalable productivity improvements. We are hopeful our work will inspire new research at the intersection of OR and life sciences. Together, we can achieve a new goal: to
drive these innovations globally and accelerate our course toward One Health. Together, we can make this world a better place for all.

**References**


