Pharmaceutical BIOPROCESSING

Analytical models for biopharmaceutical operations and supply chain management: a survey of research literature

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While sophisticated analytical tools and models for operations and supply chain management are increasingly used in many industries, the biopharmaceutical industry lags many others in terms of applying these approaches. We survey the (relatively small number of) papers that explore the use of analytical models to address various strategic, tactical and operational issues in biopharmaceutical operations and supply chain management, discuss gaps in current knowledge, and identify opportunities to further extend the state-of-the art in this area.

Keywords: biopharmaceutical • operations management • optimization • production planning • simulation • supply chain management

Over the past 30 years, analytical tools and models have made a dramatic impact on both the theory and practice of operations and supply chain management. Increasingly powerful computers combined with advanced algorithms, have enabled firms to simultaneously increase responsiveness and decrease costs in their supply chains. Raw material and finished goods inventories have been reduced while customer service levels have increased, new product roll-outs are carefully managed to fully utilize manufacturing capacity while meeting demand and controlling costs, risk management strategies hedge against demand and supply risks as well as natural and man-made disasters, long term capacity strategies are carefully designed and tested, production plans and schedules are optimized and logistics planning decreases costs while increasing on-time deliveries – overall, resources are fully and effectively utilized through the use of innovative strategies supported by detailed quantitative models, tools and algorithms [1–3]. (Indeed, over the past ten years, almost half of the finalists for the Franz Edelman Award for Achievement in Operations Research and the Management Sciences, one of the most prestigious awards given to firms for the application of analytics to business, have applied these tools to operations and supply chain management [4]). Both in our experience working with biopharmaceutical firms who are members of our National Science Foundation-sponsored Industry/University Cooperative Research Center [5], and in a recent survey of biopharmaceutical managers [6], we have observed that the biopharmaceutical industry, while it is in most ways on the cutting edge of innovation, lags many other industries in terms of the application of advanced operations and supply chain management analytics. In this paper, we augment the survey referenced above with a survey of the (relatively small number of) recently that explore analytical models for operations and supply chain management in the biopharmaceutical industry, with the twin goals of introducing these papers to practitioners, and of identifying additional research opportunities for academic research. We start by introducing the key issues that these models and tools must address.

We first observe that the position of this industry with respect to analytical tools and models for operations and supply chain management is in many ways similar to the position the semiconductor industry found itself in thirty years ago. For many years, the focus of that industry was on developing superior

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technology, with manufacturing and supply chain management as afterthoughts. However, as the industry matured and competitive pressures grew, firms focused on risk, inventory and supply chain management, leading to significant advances in the science of operations management. Biopharmaceutical firms now find themselves in a similar position. Over the past several decades, billions of dollars have been invested in the research and development of medicines, leading to groundbreaking advances in the treatment of many severe illnesses. There has been significantly less development, however, in the advancement of industry operations and supply chain management, and in particular on the development of analytical tools and models for this purpose [5].

The combination of fundamental characteristics inherent in biopharmaceutical discovery, production and distribution make the modeling and analysis of operations and supply chain management particularly challenging. These include:

- The uncertainties inherent in biological production: Yields are uncertain, and difficult to predict. Analysis takes time, which can delay production. Long testing lead times make production scheduling and efficient use of manufacturing equipment difficult. Molecules are difficult to characterize. Contamination and cross-contamination can be difficult to discover, and have difficult-to-detect characteristics;
- The difficulties associated with pharmaceutical production: regulation makes process improvements difficult, GMP requirements add to manufacturing costs, quality control testing times delay production, production failures can cost lives, and so on;
- The difficulties associated with industries where technologies and processes are changing rapidly: Planning is difficult when increasing titers (concentrations) effectively change facility capacities. Long production lead times combined with advancing technology make facility design decisions difficult. Unique production technologies may make outsourcing inappropriate. Intellectual property concerns are significant;
- The challenges associated with industries where demand is uncertain and facilities are extremely expensive: The outcome of a single trial or competitive event can drastically change capacity requirements. Capacity investment decisions are challenging in this environment. Government policies can radically alter the nature and timing of demand;
- The challenges faced by industries that outsource production, or certain production steps: production may be difficult to plan or control, and detailed production information may take some time to obtain;
- The difficulties faced by firms that must continue to track, report and even potentially stop selling products after they have started producing and selling them;
- The challenges that arise when attempting to optimize a supply chain in which different stakeholders have conflicting strategic objectives, making modeling difficult and implementation of solutions even more of hurdle.

Of course, none of these challenges are unique to biopharma – many are present to some degree in small molecule (that is, pharmaceutical non-biotech) production, and all of them appear in some form in other industries. However, this combination of challenges is unique to biopharmaceuticals, and indeed, many (but not all) of these characteristics are more pronounced in biopharma:

- Time-to-market is relatively long for biopharmaceuticals: It takes on average 10–15 years for a new biopharmaceutical medicine to complete the journey from initial discovery to the market [7–9]. This time span is about 50% longer than a typical pharmaceutical product [10], and thus important strategic decisions, such as facility construction and expansion, need to be made as early at the start of clinical trials;
- Research and development costs are relatively high for biopharmaceuticals: Recent studies show that the average R&D investment for biopharmaceutical products ranges from US$1.2 to US$1.8 billion [11–13], while the R&D cost for traditional small molecule pharmaceutical products is only approximately US$0.8 billion [14]. Overall, only two of every ten brand name medicines earn sufficient revenues to recoup R&D costs [15];
- Capacity planning is particularly challenging for biopharmaceuticals: Capacity constraints continue to be an issue for commercial-scale biopharmaceutical manufacturers. Building and licensing a new traditional commercial-scale capacity can take 4–5 years and cost up to US$800 million (see, e.g., [16,17]). Thus, it is often necessary to make capacity investment decisions early in the trial process, when there is considerable risk that the capacity will not be used for its intended pur-

pose. Even if a firm plans to produce the drug in an existing facility or outsource the product to a contract manufacturing organization, it typically takes several years and costs US$100s of millions to make necessary modifications, develop an effective approach for technology transfer and complete US FDA licensing [16]. Because biopharmaceuticals are difficult to analytically characterize, biopharmaceutical licensing is tied to the facility in which the product is made. Thus, changing or adding to manufacturing capacity after a product is licensed is expensive and risky;

- Biopharmaceutical manufacturing is uncertain and highly regulated: Because of the uncertainty inherent in the fermentation process, biopharmaceutical manufacturing is often highly variable in both output quality and quantity. Consequently, biopharmaceutical firms face the challenge of producing the target protein consistently in sufficient quantity and quality to meet demand plans. Since products often cannot be completely analytically characterized, pharmaceutical manufacturing processes tend to be very highly regulated;
- Moreover, since economies of scale combined with relatively small amounts of required active ingredients often dictate the production of multiple products in a single production facility, production scheduling is often a complex and multi-faceted process;
- Clinical trials of biopharmaceuticals are complex, time consuming and uncertain: While at 30.2% [18] the overall clinical success rate for biopharmaceutical products is about 10–15% higher than the traditional pharmaceutical products [12,19] clinical trial designs and procedures are becoming more and more complex. They cost more, take longer and have more detailed eligibility criteria [20]. Indeed, managing the clinical trial supply chain is becoming an increasingly important and complex problem [21].

In addition, firms are increasingly aware of the potential market impact as generic forms of biopharmaceuticals are beginning to be introduced into the marketplace [22].

Overall, biopharmaceuticals are not so much characterized by any single complexity that is not present in other industries, but by a large set of complexities, which combined with the life-saving nature of many products, makes the supply chain particularly challenging to manage. In spite of this, and perhaps due to the relative youth of the industry, there has been a limited amount of research focusing on the modeling and analysis of operations and supply chain-related issues within the biopharmaceutical industry, or even within the broader pharmaceutical industry. As the biopharmaceutical industry grows and matures, however, the challenging issues facing the industry are attracting more and more attention in academia. In this paper, we review recently published papers that employ analytical tools and models to address important issues in operations and supply chain management in the biopharmaceutical industry, and relevant papers with a focus on the broader pharmaceutical industry. We conclude in the section 'Future challenges' with a discussion of directions for research in this area.

Research method

To develop a comprehensive and concrete review of the recent academic research literature focusing on analytical tools and models for biopharmaceutical operations and supply chain management, we employed a three step approach:

- We conducted a rigorous literature review of analytical models and tools for operations management closely related to the bio/pharmaceutical industry;
- We categorized each model into one of three decision levels based on its focal point: strategic, tactical and operational decisions (we explain this in more detail in the section 'Key research areas');
- We carefully considered each model, focusing on the identification of unique characteristic and potential shortcomings, as well as on the similarities and difference between models that tackle analogous problems.

In the first step, we searched in Google Scholar and the Web of Science Database using combinations of keywords including 'biopharmaceutical', 'pharmaceutical', 'supply chain', 'capacity planning', 'manufacturing', 'management', 'simulation' and 'portfolio'. In addition, we identified one key relevant survey paper focusing on the pharmaceutical industry (Shah [23]). We checked the references in that survey, as well as the papers citing that survey, with a focus on papers published after 1999. Statistics cited in the sections 'Introduction' and 'Research method' above come primarily from [7]. If there are conflicting numbers, we used the most recent one.

We ultimately compiled a set of 24 journal articles and two working papers. The largest number of these papers appeared in *Industrial & Engineering Chemistry Research* (six references) and *Computers & Chemical Engineering* (five references). The remaining papers

Key terms:

Stochastic programming: Mathematical programming models that incorporate uncertainty.

Heuristic algorithms: Algorithms that find good,but not necessarily optimal, solutions to optimization problems.

Stochastic model: A model that incorporates randomness.

appeared in a variety of journals, including *Operations Research for Health Care* (two references), *Biotechnology Progress* (two references), *Chemical Engineering Research and Design* (two references) and *European Journal of Operational Research* (one reference).

Key research areas

As mentioned previously, we categorize the key relevant research areas into three decision levels: strategic, tactical and operational. By strategic decisions, we mean those that directly relate to the company's objectives and impact long-term performance. Such decisions are usually made by the highest level of management, and once executed, are extremely difficult and costly to change. Typical strategic decisions include new facility construction, existing facility expansion, facility design, product selection, capacity planning and risk management.

Tactical decisions are relatively short-term (on the order of months) decisions that support longer term strategic policy, and that define the approaches that firms use to achieve their objectives. Typical tactical decisions range from process and pipeline development to manufacturing planning, supply chain coordination and high-level campaign scheduling.

Operational decisions include the detailed daily decision making necessary to operate the biopharmaceutical supply chain. Typical operational decisions include operator assignment, detailed facility schedules, transportation plans, maintenance scheduling and detailed inventory planning.

In subsequent subsections, we survey the state-of-the-art in these areas.

Strategic decisions

Capacity planning & product selection utilizing mathematical modeling

Given the high cost, long lead times and uncertainty inherent in biopharmaceutical product development and clinical trials, the selection of a portfolio of potential projects to develop and test is critical to company's success. This same uncertainty and long development time, coupled with the high cost of manufacturing facilities and the importance of ramping up production as soon as products are approved, leads to a challenging long-term capacity planning problem. Indeed, the trade-off between deferring capacity expansion decisions to accrue more information and expediting capacity expansion to decrease time-to-market and increase effective patent life is fundamental to biopharmaceutical planning.

To address this planning problem in the pharmaceutical industry, researchers have turned to two-stage stochastic programming. The first-stage decisions in this context include product selection and initial capacity investment. Deferred second-stage decisions can utilize additional information from clinical trials as it becomes available, which includes capacity allocation, reallocation, expansion and abandonment. The second stage is typically modeled as massive number of scenarios based on clinical trials outcomes.

To illustrate this concept using a simple example, consider two products A and B, both with success probability 0.5, which results in four scenarios: Both A and B are successful with probability 0.25; A is successful but B fails with probability 0.25; A fails but B is successful with probability 0.25; and Both A and B fail with probability 0.25. In more complex settings, this example can be generalized to encompass multiple clinical trial stages, multiple products at different times, etc. Each scenario has an associated likelihood and revenue. Consequently, the natural performance measure (although by no means the only possible performance measure) when considering investment across these scenarios is expected net present value (ENPV), where a positive ENPV indicates an attractive decision, while a negative ENPV means an inefficient decision. Furthermore, the distribution of the NPV is one way to characterize the risk of a given decision.

Models based on this approach are typically formulated as mixed-integer linear programs (MILP). Given the large number of potential scenarios in most realistic settings, however, MILPs are difficult to solve to optimality. Researchers have developed a variety of heuristic algorithms to address realistic problems.

Rotstein *et al.* [24] first develop a stochastic model for simultaneous product selection and capacity planning that incorporates binary clinical trial uncertainty (i.e., success/failure). They develop a heuristic cut-off procedure to address larger size instances. This procedure selects scenarios with higher probabilities until the cumulative probability across these scenarios exceeds some predetermined level α, and then the problem is solved in this reduced scenario space. Experiments demonstrate that an α value around 0.5 yields satisfactory results while reducing the computational effort drastically. However, their proposed model is limited to the case of single-site capacity planning.

Gatica *et al.* [25] extend previous work by defining four potential clinical trials outcomes for each product

at each stage (high, target, low and failure), and modeling these scenarios in a scenario tree. An example of this type of clinical trial scenario tree with associated probabilities is shown in Figure 1. Each new potential product entering clinical trial leads to four-times more scenarios in this model, which in turn leads to a significantly more complex scenario tree (with {EQ 4\s\up5(*N*)} scenarios for *N* products) than other models with only binary outcomes. Combined with capacity expansion variables, the overall problem is formulated as a large-scale MILP, which is impractical to solve for even a small number of potential products – the examples in this paper thus consider only small numbers of products.

Papgeorgiou *et al.* [26] propose a deterministic multi-site, multi-period capacity planning model to select promising products and decide when and where to produce them and how to allocate and expand the capacity. In their model, all potential products are free of clinical trials uncertainty and they assume a known certain demand. On the other hand, this model emphasizes the importance of modeling transfer pricing and the taxation framework, as well as manufacturing details, including setup, scale-up, qualification and manufacturing suite structure. In their illustrative example, different production sites have distinct tax structures, capital costs and operating costs, all of which have the potential to significantly impact planning decisions. In contrast to stochastic models that feature exponential numbers of scenarios, this model (at least their example with seven products) can be solved using commercial integer programming software.

To incorporate the uncertainty of clinical trials, Levis *et al.* [27] extend the previous deterministic long-term multi-site planning model by explicitly including binary clinical trial uncertainty. This results in a large-scale MILP with {EQ 2\s\up5(*N*)} scenarios. The authors propose a 'hierarchical solution approach' to this problem. They first formulate a relatively small approximate model by aggregating variables related to the detailed manufacturing plan in the original model. This aggregated model mainly focus on strategic decisions such as selecting product candidates and production sites. Then they fix the solution obtained from aggregated model and solve the original detailed model in a reduced decision variable space. This hierarchical solution approach is able to find an effective solution with up to seven products using a reasonable amount of time. In all of their examples, they find this approach outperforms the cut-off procedure proposed in Rotstein [24].

Sundaramoorthy *et al.* [28,29] use a version of the model discussed above to explore the value of integrated facilities, where raw materials through the active

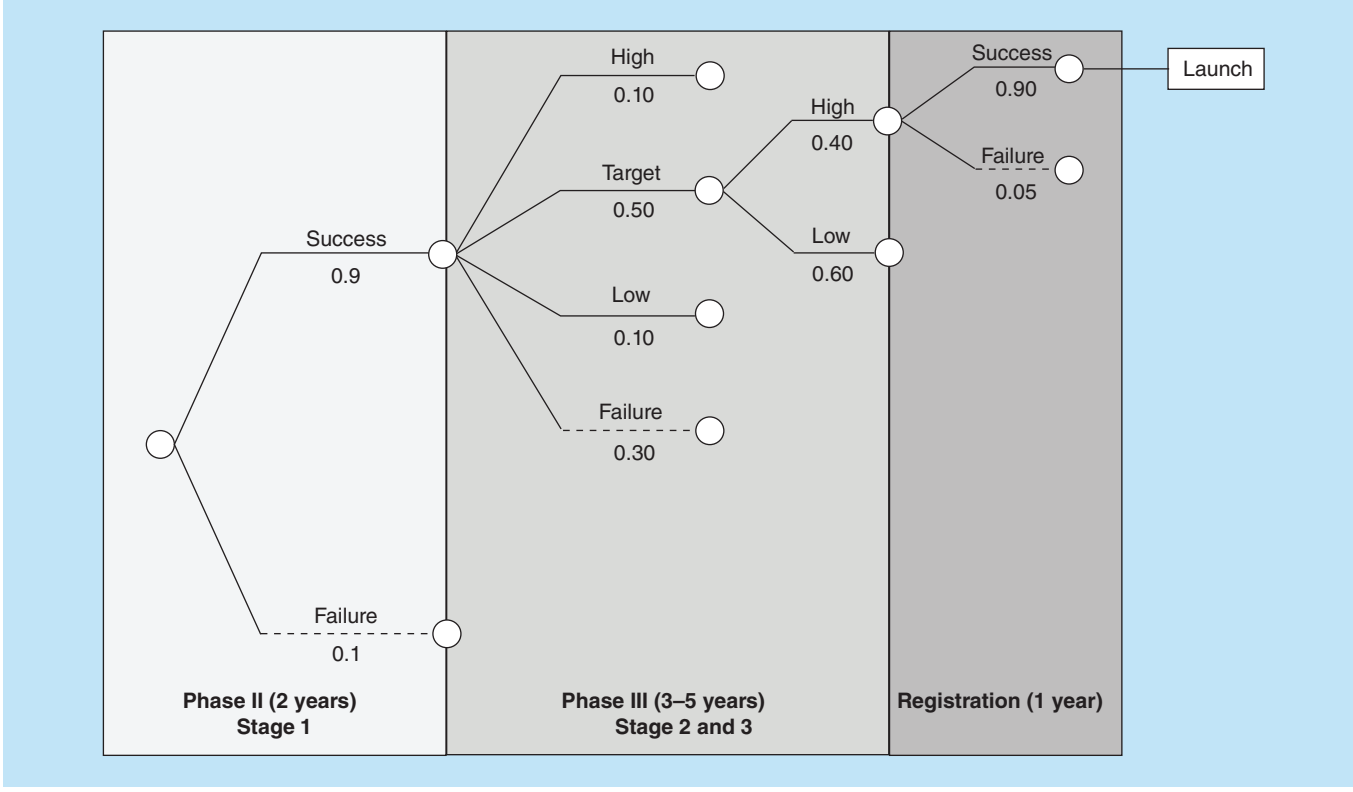

Figure 1. Tree representation of clinical trails outcomes.
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Key terms:

Mathematical programming: A set of techniques to solve optimization models.

Optimization: A set of mathematical techniques for finding the minimum or maximum value of a function possibly subject to a set of constraints. An optimization model of an industrial problem expresses that problem mathematically so that the tools of mathematical programming can be used to solve it.

ingredients to final products are processed seamlessly within a single facility. This is an approach used in pharmaceutical manufacturing, although not yet to our knowledge in biopharmaceutical manufacturing. Researchers have found that this continuous approach can save 9–40% over traditional batch manufacturing (see Schaber [30]). They formulate this capacity planning problem as large scale MILP with 2^N scenarios, and utilize a hierarchical solution approach using a duality-based decomposition method, called nonconvex generalized Benders decomposition. Using the nonconvex generalized Benders decomposition algorithm, they heuristically solve instance up to 16 products.

Overall, these papers introduce the use of powerful mathematical programming tools to optimize product selection and capacity planning decisions. However, even within the context of applied mathematical programming, there are a variety of potential research directions that as yet have not been pursued. All of these papers focus on pharmaceutical production, rather than on biopharmaceutical production, and so many of the key characteristics of biopharmaceutical manufacturing, including process specifics, production uncertainties and the outsourcing of parts of the production process, have not yet been modeled. In addition, these kinds of models could be extended to capture issues such as supply chain risk and disruption mitigation, product roll-out issues, time-varying demand due to markets where products are sold in response to tender offers, and so on. Finally, a variety of new mathematical programming-based approaches have been introduced in recent years to model and solve similar problems in related industries, including sample average approximation and robust optimization (see [31–33], and references therein).

Capacity planning & product selection utilizing simulation

As an alternative to mathematical programming approaches, simulation-based approaches can be used to characterize in more detail the risk inherent in product selection decisions. Instead of focusing on detailed capacity planning at the commercial-level manufacturing stage, most of the papers we review in this subsection focus more on the selection and sequencing of drugs at the development and trial stages, where optimizing product portfolio risk is most critical. Since limited manpower, capital and equipment resources prevent firms from concurrently developing a large number of potential products, the sequence in which drugs enter the development pipeline have a significant impact on the firm's profits. The problem is further complicated by the dependencies among candidate drugs. In contrast to optimization-based approaches, however, simulation approaches are descriptive – they can be used to analyze the risk inherent in any particular decision, but they must be combined with detailed experimental designs to assess the optimal values for decision variables.

Blau *et al.* [34] study the problem of product selection and development sequencing while managing risk. Input data for each potential product focuses on three key sets of characteristics: clinical trials success probabilities, development capital cost and sales if the product passes clinical trials. A bubble chart combining all of these characteristics (see Figure 2) is used to screen out unpromising products. The position of each bubble is determined by the corresponding product's mean reward/loss ratio and success probability, while the size of the bubble is proportional to the resources required to develop the product. By accounting for the firm's attitude toward risk, a portfolio can thus be selected. After products are selected, a simple heuristic approach using Monte Carlo simulation is employed to sequence the portfolio in the pipeline. Different sequences are compared based on their ENPV. One drawback of the proposed approach is its inability to explicitly enforce resource constraints. To address this, the authors propose to track resource constraint violations, but the firm must decide if those violations are acceptable.

Rajapakse *et al.* [36] develop a computer-aided tool using Monte Carlo simulation that models the risk and the rewards of alternative strategies for biopharmaceutical drug development and portfolio management. The tool is built around a hierarchical framework that integrates resource management, manufacturing activities and clinical trials. The tool is employed in a case study, where the impact of a variety of different parameters and scenarios are explored. For instance, for the case explored in the paper, the tool is used to demonstrate that of the possible manufacturing strategies, outsourcing production is the least risky strategy due to capital savings. These savings in this case outweigh the risks associated with using a CMO, such as delays in negotiation and material delivery.

Later, Rajapakse *et al.* [37] extend this simulation-based modeling framework to aid in portfolio selection. In contrast to the more *ad-hoc* approach described

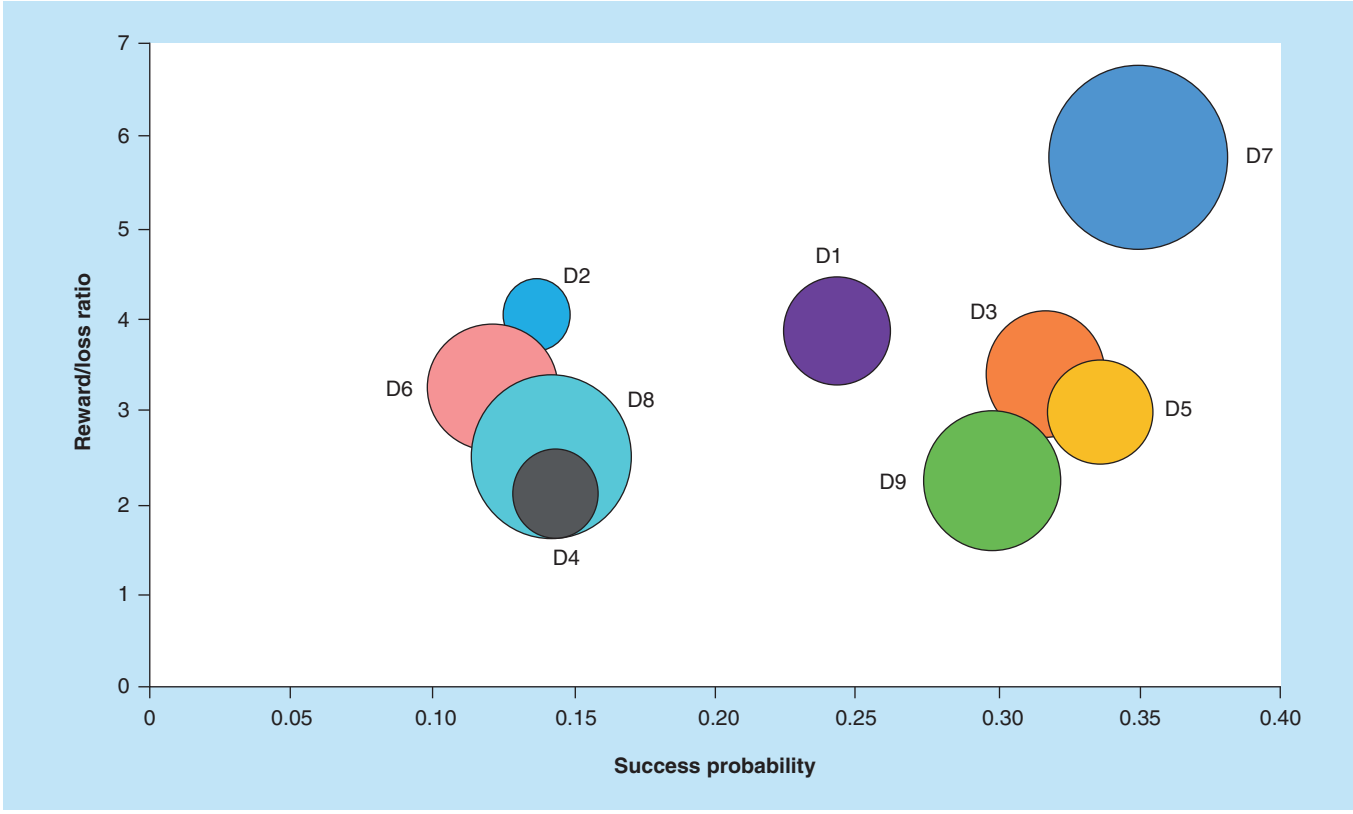

Figure 2. Sample bubble chart for all candidate products.
Reproduced with permission from [35].

in Blau, Rajapakse utilizes Monte Carlo simulation to characterize the efficient frontier (see Figure 3) of ENPV and risk (standard deviation of the NPV distribution) for portfolios selected from a set of possible candidate drugs. Any portfolio that lies on the efficient frontier is a candidate for selection, but the final decisions will be a function of the firm's risk profile. In computational studies, the authors demonstrate most interestingly that given a higher resource level, increasing the number of products in a portfolio could negatively impact both ENPV and risk level.

Blau *et al.* (2004) [38] study product selection and sequencing with a particular focus on modeling the dependencies among various development activities, including resource dependencies, manufacturing cost dependencies, financial return dependencies and technical success dependencies. For example, if more drugs targeting the same disease are successfully developed, then the profit for each drug will be lower. This paper is also the first we are aware of in this problem domain to combine simulation and heuristic optimization: simulation is used to obtain the NPV and its distribution given a selection of candidate drugs and their sequence to enter the pipeline, and a single-objective genetic algorithm is used to optimize the product selection and sequencing. This approach improves the ENPV by 28% when compared with the sequence suggested by the bubble chart approach, but the proposed simulation-based method is computationally demanding. It takes about 60 h for the algorithm to examine 1000 sequences. One intriguing result shows that the ENPV of portfolios that lie on the efficient frontier first increases and then decreases as the risk increases, in other words, the efficient frontier is not monotone. The authors conclude that the traditional insights of financial portfolio management do not apply in biopharmaceutical industries because of interdependencies.

Based on the discrete event simulator presented in the previous paper, Pérez-Escobedo *et al.* [35] introduce an innovative interval analysis to tackle the uncertainties inherent in the product sequencing. This approach aims to quantify uncertain model parameters using intervals rather than random variables. For example, in the previous paper using probabilistic approach, Phase I cost is modeled as a triangular distribution from 70 to 90 with most likely value 80 (M$). In contrast, the interval-based approach simply represents the Phase I cost by (76, 83) (M$), the interval of possible values. However, the interval analysis approach is unable to incorporate failure probabilities from clinical trials stage. In addition, results from the interval approach are

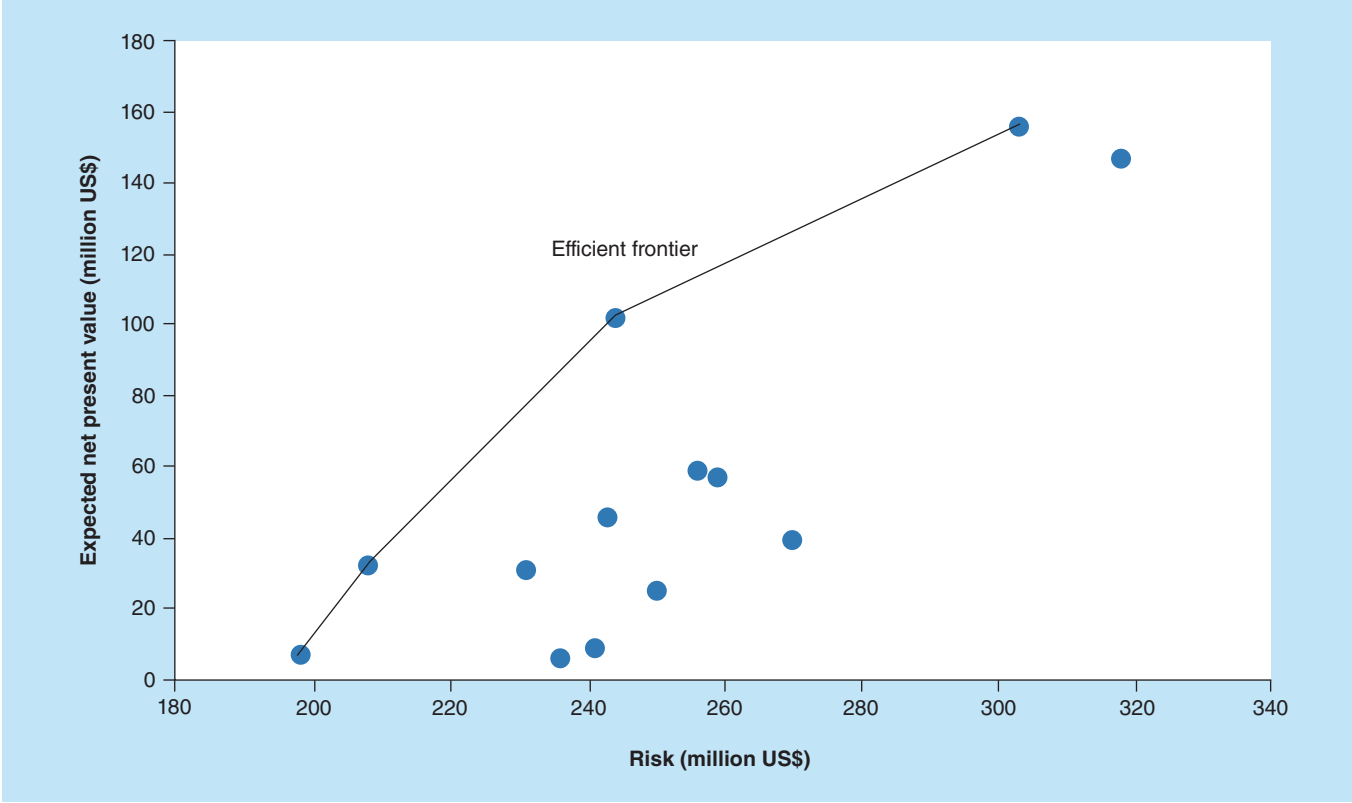

Figure 3. Using efficient frontier to select portfolio.
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also intervals, making it difficult for decision makers to tell which drug is actually better. Hence the authors conclude that traditional probabilistic approaches are preferable.

As mentioned above, the majority of the papers considered in this subsection focus on portfolio selection – there is ample opportunity to use the same types of tools and approaches to more explicitly consider the details of capacity planning and acquisition within the biopharmaceutical industry. In addition, recent developments in simulation optimization, including sophisticated statistical approaches for ranking different options, gradient approximation methods for optimization of parameter settings and techniques for rapidly completing large numbers of simulation experiments, could likely be beneficially applied to biopharmaceutical planning problems (see [39] and references therein).

Tactical decisions

Manufacturing planning & campaign scheduling

In terms of tactical production planning, biopharmaceutical manufacturing shares a number of key characteristics with small molecule pharmaceutical and other chemical manufacturing processes, particularly those that take place in multi-purpose facilities where production is divided into campaigns of multiple consecutively produced batches of the same product. However, in the highly regulated biopharmaceutical industry, significant time and resources must be devoted to changeovers between campaigns of different products, making campaign scheduling particularly crucial for efficient capacity utilization. Also, because intermediates are often unstable and products are typically perishable, product lifetime plays an important role in planning.

Sequencing and campaign scheduling for batch manufacturing has long been studied in chemical manufacturing (see Shah [40] and Papageorgiou [41]). Artiba *et al.* [42] considers the case of a parallel multi-product and multi-machine production planning problem in a pharmaceutical manufacturing plant. Focusing specifically on a biopharmaceutical context, Lakhdar *et al.* [43] consider medium term (1–2 years) planning for a multiproduct biomanufacturing facility with the goal of maximizing operating profit. They model details of biomanufacturing processes including fermentation and purification, and use their model to determine campaign durations and sequences. Following the approach used in nonindustry-specific models, they formulate the problem as MILP, and use this formulation to optimize several examples with

suite-specific manufacturing and differing production throughput rates. They compare their solutions to simple experience-based industrial rules, and are able to improve profitability from 13–40%. Lakhdar *et al.* [44] builds on the models developed previously in order to consider multiple facilities and multiple objectives – cost, service level and capacity utilization. These (potentially) conflicting objectives results from the differing concerns of different supply chain stakeholders. The authors adopt a goal programming framework, where the mathematical programming objective is to minimize deviations from targets for each of the objectives.

The campaign planning models discussed to this point consider deterministic production and demand; Lakhdar *et al.* [45] modify the deterministic medium-term planning model presented in Lakhdar [43] to account for uncertain fermentation titer, a critical driver impacting both the cost of manufacturing and production throughput in biopharmaceutical manufacturing. The authors model the variable production rate using three discrete levels: low, medium and high, and assume that the true rate is revealed at the beginning of the planning horizon, so that the problem can be formulated as a two-stage stochastic MILP with 3^N scenarios. An iterative heuristic algorithm is proposed for realistic-sized problem with ten products and 18 time periods. The heuristic algorithmic saves considerable computational time relative to optimally solving the stochastic MILP, while finding a better solution than the solution found by the deterministic model.

As with research focusing on applying mathematical programming to product selection and capacity planning, there is opportunity to extend mathematical programming-based modeling of planning and scheduling models to capture more key characteristics of biopharmaceutical operation, including demand uncertainty, cost uncertainty, contamination events, outsourcing, disruptions, etc. In particular, risks of all kinds can be modeled in more detail, and alternative solutions can be presented with associated risk profiles. Again, mathematical programming-based approaches such as sample average approximation and robust optimization might prove fruitful if these lines of research are pursued.

In addition, the emergence of novel production approaches and technologies, such as disposable production trains and perfusion production, suggests the need to extend existing planning and scheduling models, and to develop new ones. For example, Bu *et al.* explore planning in the context of semi-batch perfusion processes, a technology that is increasingly used in biopharmaceutical manufacturing [Bu D, Kaminsky P. Production lot sizing with immediately observable random production rate. Working paper, Department of Industrial Engineering and Operations Research, University of California, Berkeley (2014); submitted]. The authors develop and compare a series of heuristics intended to determine when to 'cut-off' processing of an individual 'batch' and when to switch between different products.

Supply chain coordination

While the bulk of tactical level biopharmaceutical operations papers focus on production and campaign planning and scheduling, there are a variety of other tactical issues that researchers are beginning to explore. For instance, Meijboom *et al.* [46] investigate the supply chain of an internationally operated pharmaceutical company. Using an integer programming model, the authors compare two potential organizational structures for the company, functional unitary form (U-form) and multi-divisional form (M-form). In the U-form organization, the company is divided based on its three basic functions: supply, production and distribution, and decision making is centralized, while the M-form company is divided geographically, and decisions are made within each of its division. In their case study with a pharmaceutical firm, the authors show that the M-form firm is easy coordinate using a transfer pricing mechanism, while the U-form organization is more difficult to coordinate.

Operational decisions

Inventory management

Even fewer authors explicitly consider operational decision making in biopharmaceutical manufacturing and supply chain, perhaps reflecting the traditional lack of emphasis on optimizing operational decisions within the industry.

Boulaksil *et al.* [47] study the problem of determining safety stock levels in a complex multi-product multi-stage supply chain, and develop an approach that solves a rolling horizon MILP in a simulation setting. Combined with the results of multiple simulation runs, the proposed approach is used to determine effective safety stock levels in order to achieve desired customer service levels. The authors describe an implementation of their approach at a biopharmaceutical firm, where they are able to decrease the safety stocks by 20–50% from the current setting while maintaining desired customer service levels.

Using an approach called Retrospective Optimization Integer Programming (ROIP), Kaminsky and Liu [48] address similar biopharmaceutical inventory control parameter setting problems. ROIP uses an integer program to optimize inventory parameter settings along a sample path. The authors demonstrate the effectiveness of this approach in biopharmaceutical

supply chain settings. While very complex supply chain settings lead to big, difficult to solve integer programs, the authors develop an approximate approach based on stochastic gradient search methods. A numerical study demonstrates that a hybrid approach that combines integer programming with stochastic gradient search can reduce solution times from over 20 h to just a few seconds while finding solutions that are a fraction of a percent away from the solutions found by the integer program.

Another stream of research focuses on inventory modeling in the downstream portion of the pharmaceutical supply chain (i.e., a hospital or clinic) using mathematical modeling. Baboli *et al.* [49] investigate replenishment policies between a warehouse and a hospital, focusing on comparing centralized and decentralized replenishment approaches accounting for transportation costs. The authors develop heuristics to determine the timing and quantity of orders, and compare the performance of these heuristics. In their numerical experiment, they show a 24% saving for centralized replenishment policy. Kelle *et al.* [50] focus on pharmaceutical inventory management in a single care unit, and propose a multi-product inventory management model using an (s, S) policy for each product. The full model with consideration of product volume and space constraints proves difficult to solve, so the authors develop several simplified models. The authors demonstrate that implementing these simplified models can result in reduction in inventory expenditures of up to 80%.

As firms become increasingly focused on efficiency and cost–effectiveness, there are many more opportunities to develop model-based approaches to improving operational decisions. Detailed scheduling models, labor utilization tools, delivery coordination, detailed process and operations simulation, logistics optimization, etc., all present opportunities to adapt and modify tools, techniques and approaches that have proved fruitful in many other industries to account for the details and complexity of biopharmaceutical operations.

Future challenges

Our goal with this survey was to highlight existing literature with a hope of making it more accessible to practitioners, and clarify research opportunities with respect to developing and applying analytical tools and models to biopharmaceutical operations and supply chain management. As we discussed above, however, there is relatively little relevant published research that will be useful to practitioners, and many opportunities for researchers to develop tools and models to address important industry problems. Throughout this survey, we have identified specific knowledge gaps and future research opportunities. At a strategic level, for example, in the context of mathematical modeling-based tools for capacity planning and product selection, there is opportunity to capture more of the details specific biopharmaceutical processing, including specific process characteristics, as well as the details of commonly used supply chain structures (e.g., in-house manufacturing with outsourced filling and labeling.) Simulation-based strategic tools can similarly be generalized to more explicitly capture details of biopharmaceutical processes and supply chains, and in particular the various sources of variability and uncertainty that are specific to biopharmaceutical production.

At a tactical level, scheduling and planning models can be extended to capture critical biopharmaceutical production characteristics, by modeling demand and production uncertainty, contaminations, quality assurance-related delays and the impact of outsourcing, and by presenting alternative solutions with different risk profiles.

Finally, at the level of operational decision making, little has been published. Several papers explore inventory optimization in biopharmaceutical supply chains, but there is ample opportunity to develop that tools that will optimize day-to-day scheduling, and labor and resource allocation.

There are many other related areas where novel developments could make an important contribution to the industry. As novel technologies such as disposal processing equipment and continuous processes becoming more prevalent, a variety of strategic, tactical, and operational issues around investment in, acquisition of, and use of, these technologies needs to be addressed. As Quality by Design (QbD) becomes more prevalent, flexible operations will be increasingly necessary to ensure efficient batch release [51]. As the risk of supply chain disruption, and the importance of effectively managing this disruption, become more evident, tools and analyses that address operational issues around supply chain risk become more critical. As products increasingly serve smaller and smaller populations, and as the nature of clinical trials and initial product roll-out changes [52], tools to manage operations in this environment will turn to be more crucial.

In addition, the increasing availability of large amounts of data is presenting challenges and opportunities to most industries, and the biopharmaceutical industry is no exception. Detailed process, production, logistics, data and demand data can lead to more efficient production and supply chain operations, but there is far too much of this data to analyze by hand – sophisticated tools will be necessary.

These are all difficult problems. However, from a technology standpoint, recent developments in the

tools of optimization and simulation have great promise for addressing the problems of the industry. Optimization software continues to get faster more powerful, and the technology for incorporating uncertainty into optimization models is becoming more and more sophisticated, with the increasing development of techniques such as sample average approximation and robust optimization. A variety of approaches for simulation optimization, including novel approaches for ranking and selection of alternatives, gradient-based search methods for variable optimization, are increasingly being refined, and even incorporated into commercial software. Finally, tools that work with larger and larger sets of data are entering the mainstream. Very few of these concepts have been applied to biopharmaceutical operations, and we suspect that great strides will be made as they are applied in the future.

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Executive summary

Background

- The biopharmaceutical industry has a unique set of operations and supply chain challenges.
- The biopharmaceutical industry lags behind other industries in applying advanced analytical tools and techniques to address these challenges.

Research method

- A comprehensive survey of the recent academic research focusing on analytical tools for biopharmaceutical operations and supply chain management was completed.

Key research areas

- A strategic level, existing model-based operations and supply chain management research explores the use of optimization and simulation tools for capacity planning and product selection.
- At a tactical level, existing literature analyzes planning, campaign scheduling and coordination issues.
- Operations-focused work explores supply chain inventory decision making.
- Opportunities exist to investigate the use of novel mathematical programming techniques that have been developed to model and optimize supply chains in other industries, to extend models to capture more of the characteristics of the industry, to address issues of risk mitigation and to integrate optimization and simulation, among others.

Future challenges

- Many industry problems have yet to be addressed in a rigorous, analytical and model-based fashion.
- As more data becomes available, the opportunity to make data-driven decisions is becoming more readily available, but tools must be developed to do so.

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