Meeting Future Patient Demand for Drugs in Development Now

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Key Insights

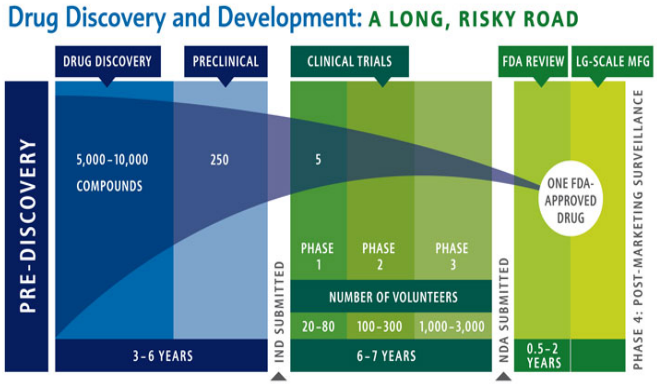
1. Early stage molecules in development have a high degree of risk and uncertainty, complex manufacturing processes, and many levels of regulatory hurdles.
2. Changes to input parameters influencing the drug development process is inevitable. Therefore, any model used to simulate the process has to be readily adaptable and modifiable.
3. Individual parameters or combination of parameters impact anticipated manufacturing production quantities for drugs differently, and these can be observed and measured through simulation.

Summary
Working with a large global pharmaceutical company, research was conducted to develop a model that assesses future manufacturing capacity risk for drugs in their early stages of development. A discrete event simulation model was built to simulate active pharmaceutical ingredient production quantity outputs given varying levels of stochastic parameters. Results can be used to better inform capacity planning decisions.

Introduction
Supply chains in the pharmaceutical industry are growing increasingly more complex and expanding their geographic reach both in manufacturing production and to the end consumer, the patient. Physical development, manufacturing and distribution of these drugs, both of biologics and small molecules, is extremely technical. The industry is highly regulated with nuanced requirements that vary by country of origin and consumption, adding complexity to the drug development process. For these reasons, companies are pushing for longer range planning and forecasting of their drug pipelines, beginning the process earlier for drugs that are in pre-clinical phases of production in order to adequately plan for capacity in manufacturing and distribution.

According to the sponsoring company, increasing capacity through building a new manufacturing site can take up to 10 years due to regulatory hurdles. The industry rate of companies passing FDA requirements for manufacturing quality inspections has held in the range of only 50% over the years. Investments into capacity and capabilities are made early with limited information about the drug.

Being able to better assess manufacturing risk allows for more informed decisions on expanding or modifying capacity. This ensures the ability to meet future patient demand for drugs in development now.



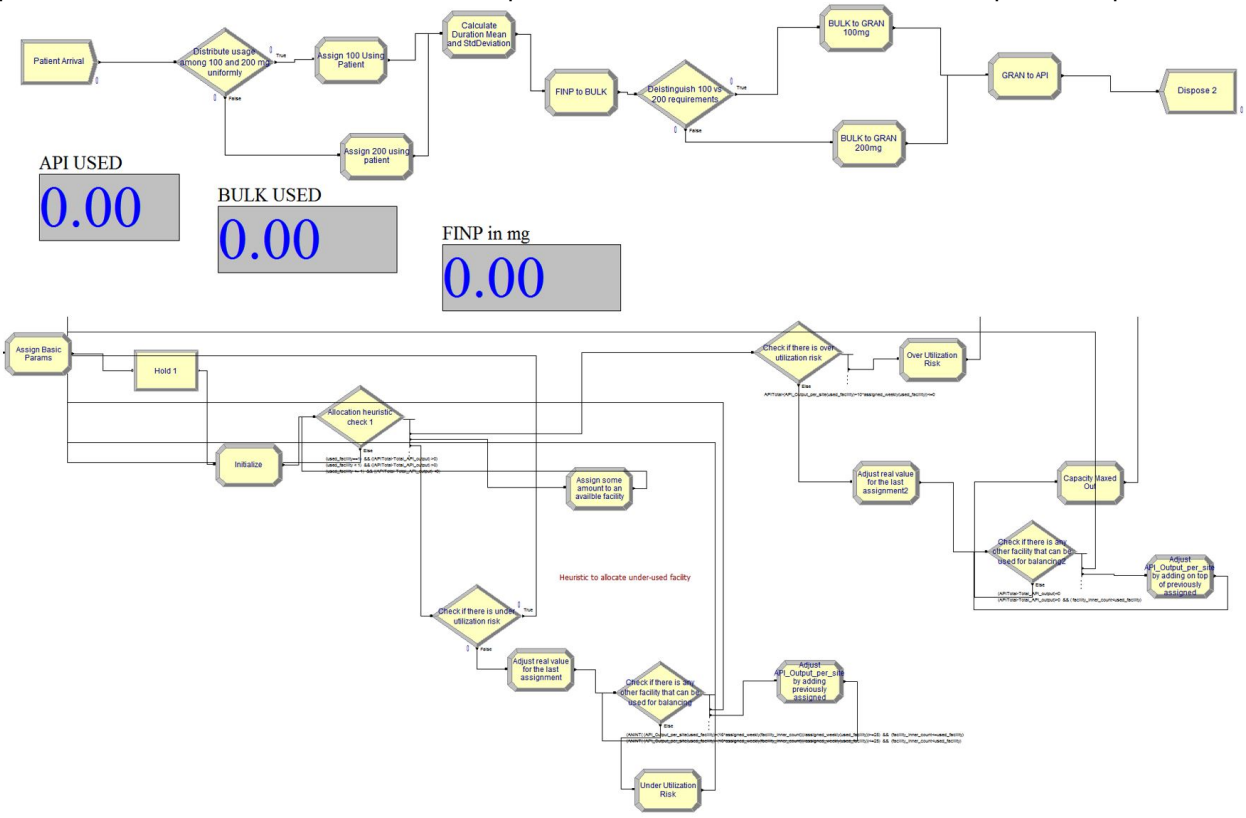
Working with data on molecules across different lines of treatment in the drug development pipeline, a discrete event simulation model was developed to simulate production quantity outputs. Levels of stochastic parameters were varied such as drug dosage, treatment duration, patient population, patient compliance, and competitive market share.

Simulation Methodology
Several simulation model methods were considered.

A System Dynamics (SD), Discrete Event Simulation (DES), and Monte Carlo approach were considered. Given that the Monte Carlo method is the currently used method for the sponsoring company, other systems modeling techniques were prioritized and considered for purposes of differentiation and novelty. Therefore, between SD and DES, the linearity of decisions and events favored DES over a system dynamics approach, also referenced in the literature review when comparing modeling techniques. System dynamics is good for continuous relationships where relations between inputs and outputs are modeled and defined without discrete increments. In this model however, every patient changes the system discretely so DES was favorable.

Model Structure

The model is designed in Arena software as a series of processes of modules which are assigned attributes and flow through a number of decision variables to generate outputs into a file for analysis performed in excel or R. The model is set up for each run with a determined set of replications per run.



The model is initialized first by patient arrivals, which are obtained in ranges by year from information provided by the sponsoring company and a distribution applied to the initial patient population in year one. The time horizon is defined, for example the model generates output for ten years. Patients are then assigned possible dosages, where distributions are varied. The remaining parameters that impact annual demand are then applied in the “assign basic parameters” module. This module includes the remainder of stochastic parameters: duration, compliance, and market share.

Manufacturing conversion units supplied by the sponsoring company on the specific drug manufacturing requirements are used to convert the FINP units to API. Active Pharmaceutical Ingredient (API) quantities are the desired output in this stage of the model to feed into the manufacturing risk assessment scheme. This stage of the model imitates the heuristic at allocation of API production to available manufacturing sites.

The “allocation heuristic check 1” is the step in the model where the API output desired by patients is compared against the network availability to manufacture the API output in one or more facilities based on each facility’s resource-hours in API production. The company sets a target capacity, maximum capacity, and minimum capacity.

There are three main cases the model assesses:
Case 1: Capacity is maxed out: After allocating maximum capacity of production to all eligible facilities, additional production capacity is needed.

Case 2: Capacity is over-utilized: After allocating target capacity load to each facility, some of the sites are required to be run between target and maximum, which is over the target utilization. However, API demand can be met with existing facility and resource network.

Case 3: Capacity is under-utilized: Any existing facility needs to be run at less than minimum capacity production load, after allocating the minimum capacity to usable sites. The total number of used facilities must be less than the available number of facilities. Therefore, one or more sites need to be run under minimum production targets.

Each of the following cases are given a risk rating value during analysis to come up with an aggregate manufacturing capacity risk measurement as a sum of these ratings for each replication.

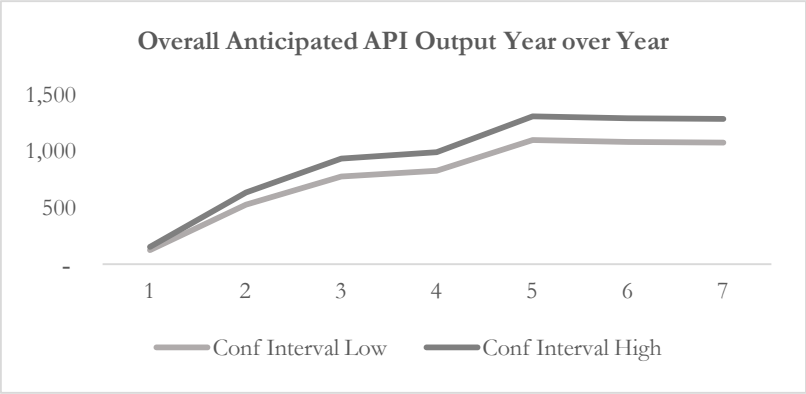
Manufacturing Risk Ratings
Each of the scenario outputs were given a risk rating based on impact to overall manufacturing capacity network. These risk ratings are used to perform analysis of variance (ANOVA) tests on parameters.

Risk rating 0: Demand is satisfied by at least target allocation to all available sites
Risk rating 1: Demand is satisfied while running some sites at under minimum capacity
Risk rating 2: Demand is satisfied while running some sites at maximum capacity
Risk rating 5: Demand is not satisfied while running all sites at maximum capacity

Analysis of Outputs and Results
Two sets of analysis were performed in excel on the results obtained from the model.

The first was to obtain 95% confidence interval levels from varying all variables, then one variable at a time holding other constant. Variables are randomly tested within the ranges. The purpose was to observe the magnitude and the direction of how the low and high levels of the interval change with each variable. In these tests, each replication for a variable was run with 100 replications and generated 7 years of data per replication. The mean and standard deviation of the API output specifically were calculated for each year of all of the replications, so for example, all year 1 of each replication. The z-score used was 1.96, which corresponds to a 95% confidence interval.

This produced results that could be visualized graphically to demonstrate anticipated API output.



The second was to perform a sample set of two-way ANOVA tests to assess the combined effect of parameters. The basic assumptions of ANOVA were assumed in terms of normality, independence, and homogeneity. A combined risk value for each replication was determined for each combination of levels of parameters.

Calculations were performed as per typical ANOVA specifications. Grand mean, total variation, between group variation, within group variations were calculated. Mean square is the sum of squares divided by its degrees of freedom, and the F-value is the ratio of the mean squares. The critical F-value was calculated for a 95% confidence interval. The null hypothesis is rejected if the F-statistic calculated is greater than the F critical value generated.

Results from these tests were used to provide insights into the degree of influence that parameters and interactions of parameters have on manufacturing risk values. These results can guide management as to which parameters to focus on more than others.

Conclusion

Pharmaceutical companies make big bets on manufacturing capacity requirements on a drug development pipeline with extremely limited information and in a regulatory environment that does not allow for a high degree of agility.

The model is intentionally readily customizable in the event of changes of information about inputs like obtaining additional data to narrow or broaden the variability of parameters, a likely situation during the drug development process. Additionally, the model serves as a framework to simulate demand and manufacturing risk for other pre-phase III drugs in development and was built to be unspecific to a particular product. More broadly, the model could be adjusted and applied generally to assess new product development manufacturing risk beyond the pharmaceutical industry.

The thesis demonstrates that the manufacturing capacity risk and demand of the drug development process for early stage molecules can be simulated through a flexible and adaptable model.