Strategic Capacity Planning for Biologics Under Demand and Supply Uncertainty

By Sifo Luo

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Agenda

• Industry Background
• Problem Statement
• Optimization Model
• Results
• Implications
Agenda

Industry Background
  • Biologics and Long Range Planning
Problem Statement
Optimization Model
Results
Implications
What Are Biological Products?

Small Molecule Drugs
Organic or chemically synthesized, such as Aspirin

Big Molecule Products
Made from biological systems, based on proteins that have a therapeutic effect, often used in cancer treatment

VS.

Herceptin (breast cancer)
Biologics Drugs Need Long Range Planning

- Lengthy approval process for new product
- Every process of manufacturing and distribution is heavily regulated
- Complicated supply chain prolongs lead time
The Ultimate Goal of Biologics Supply Chain

Supply Continuity
Agenda

Industry Background

Problem Statement
  - Capacity Planning in XYZ Co.
  - Research Question

Optimization Model

Results

Implications
Demand Planning Drives Supply Planning

Market Demand

- Number of Patients
- Drug Dosage
- Therapy Duration

Product Demand in Volume

Units of Vials/Capsules/Tablets

Kilograms of API (Drug Substance)

Manufacturing Demand
Current Capacity Planning Process in XYZ Co.

Simplified biologics supply chain

**Capacity planning flow**

- **Drug Substance Capacity Allocation**
  - Conversion Factor = Success Rate * Kgs per Run * Runs per Weeks

- **[API] Drug Substance**

- **[Bulk] Drug Products**
  - Filling Throughput

- **[Finp] Packaged Products**
  - Packaging Throughput

= **Products in Vials/Capsules/Tablets**
At XYZ Co., these parameters of the production facilities are kept at constant expected self-reported values in capacity planning.

<table>
<thead>
<tr>
<th>Success Rate (SR)</th>
<th>Kilograms per Run (KGS)</th>
<th>Runs per Week (RW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected ratio of runs (batches) that are successfully made</td>
<td>The average production volume expected from a batch</td>
<td>How many batches the site can run</td>
</tr>
</tbody>
</table>
What Does That Mean?

When conducting new product capacity planning, the company only takes into account the market demand variation, but manufacturing variability is omitted in the planning process.
Research Question

Can varying the aforementioned manufacturing parameters significantly affect production allocation and capacity utilization? If so, how significant?
Incorporate Manufacturing Performance in Supply Planning

1. API
2. Production Sites
3. Manufacturing Parameters
4. Future Years
Agenda

Industry Background
Problem Statement

Optimization Model
  • Model Parameters and Scenarios
  • Decision Variables
  • Objective Functions
  • Model Constraints

Results
Implications
## Optimization Model Parameters

Demand of drug substance, in kilograms

**Base case**: the most likely expected-demand scenario

**Downside**: lower 10% range of the demand forecast

**Upside**: upper 10% range of the demand forecast

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Demand Basecase</td>
<td>Drug X</td>
<td>API 1</td>
<td>140.0</td>
<td>155.3</td>
<td>153.1</td>
<td>130.9</td>
<td>111.9</td>
<td>113.5</td>
<td>99.5</td>
<td>126.9</td>
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<td>API 1</td>
<td>223.1</td>
<td>246.8</td>
<td>280.9</td>
<td>288.3</td>
<td>270.5</td>
<td>279.5</td>
<td>248.1</td>
<td>343.8</td>
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<td>API 1</td>
<td>267.6</td>
<td>267.2</td>
<td>193.7</td>
<td>149.3</td>
<td>128.6</td>
<td>130.8</td>
<td>115.3</td>
<td>143.4</td>
</tr>
</tbody>
</table>

**Base Scenario Annual Demand**: 630.8, 669.3, 627.6, 568.4, 511.5, 523.8, 462.9, 614.0

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<thead>
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</thead>
<tbody>
<tr>
<td>Demand Downside</td>
<td>Drug X</td>
<td>API 1</td>
<td>93.3</td>
<td>137.0</td>
<td>107.1</td>
<td>80.1</td>
<td>67.2</td>
<td>61.9</td>
<td>59.7</td>
<td>29.3</td>
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<tr>
<td>Demand Downside</td>
<td>Drug X</td>
<td>API 1</td>
<td>193.6</td>
<td>203.4</td>
<td>214.8</td>
<td>198.6</td>
<td>176.0</td>
<td>179.5</td>
<td>157.1</td>
<td>216.5</td>
</tr>
<tr>
<td>Demand Downside</td>
<td>Drug X</td>
<td>API 1</td>
<td>230.8</td>
<td>212.4</td>
<td>145.9</td>
<td>107.4</td>
<td>87.9</td>
<td>86.8</td>
<td>75.5</td>
<td>93.2</td>
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</tbody>
</table>

**Downside Scenario Annual Demand**: 517.7, 552.8, 467.9, 386.1, 331.1, 328.2, 292.3, 338.9

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<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Demand Upside</td>
<td>Drug X</td>
<td>API 1</td>
<td>185.0</td>
<td>175.0</td>
<td>166.8</td>
<td>178.8</td>
<td>151.2</td>
<td>133.8</td>
<td>103.3</td>
<td>161.0</td>
</tr>
<tr>
<td>Demand Upside</td>
<td>Drug X</td>
<td>API 1</td>
<td>251.2</td>
<td>295.2</td>
<td>366.2</td>
<td>414.4</td>
<td>422.7</td>
<td>446.3</td>
<td>396.1</td>
<td>550.1</td>
</tr>
<tr>
<td>Demand Upside</td>
<td>Drug X</td>
<td>API 1</td>
<td>309.1</td>
<td>337.1</td>
<td>278.5</td>
<td>255.7</td>
<td>256.2</td>
<td>279.1</td>
<td>245.1</td>
<td>303.9</td>
</tr>
</tbody>
</table>

**Upside Scenario Annual Demand**: 745.3, 807.3, 811.5, 848.9, 830.0, 859.2, 744.5, 1,015.0

Annual demand requirement of drug X, in kilograms
## Optimization Model Parameters

### Manufacturing Parameters

<table>
<thead>
<tr>
<th>Parameter Scenarios</th>
<th>Success Rate ($SR$)</th>
<th>Kilograms per Run ($KGS$)</th>
<th>Runs per Week ($RW$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upside Range</td>
<td>Base Case * (1 + 10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Downside Range</td>
<td>Base Case * (1 – 30%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Scenario Schema

18 scenarios are generated when only varying one manufacturing parameter at a time

3 Demand Scenarios

 upset  \[\rightarrow\] \[\rightarrow\]  Success Rate Upside

 Base  \[\rightarrow\]   \[\rightarrow\]  Success Rate Base

 Downside  \[\rightarrow\]   \[\rightarrow\]  Success Rate Downside

2 Success Rate Scenarios

 Runs per Week Base

 Kilograms per Run Base

Example scenario generation process for \textit{success rate}, while the other two parameters are kept at base values
Production Capacity

Capacity of manufacturing facilities is measured in weeks.

Example Production Allocation

- **Full Capacity**: 52 Weeks
- **Target Capacity**: 41.6 Weeks
- **Minimum Capacity**: 26 Weeks
- **Baseloads**
Objective Function:

\[
\text{Min } \sum_{M,T,API,DL,S}(XW^+_{m,t,api,dl,s} + XW^-_{m,t,api,dl,s} + U1 * P_{m,t,api,dl,s}) + U2 * \sum_{T,API,DL,S}(\text{ExtraThput}_{t,api,dl,s} + \text{SlackThput}_{t,api,dl,s})
\]

**Part 1: Capacity Allocation**

minimizing the deviation from the target capacity level

**Part 2: Site Selection**

minimizing the sites used

**Part 3: Demand Fulfillment**

minimizing the unsatisfied demand and excess production respectively
This Model is Subject to Three Main Constraints

Constraint 1: Capacity Conversion

Capacity = \frac{\text{Production Volume}}{\text{SR} \times \text{RW} \times \text{KGS}}

(\text{the denominator value is changing per scenario})

Constraint 2: Demand Requirement

The annual production volume across sites needs to satisfy the annual demand

Constraint 3: Capacity Bounds

Minimum Capacity Level ≤ Capacity
Allocated to New Product + Existing Production ≤ Full Capacity Level
Agenda

- Industry Background
- Problem Statement
- Optimization Model
- Results
  - Effect of Demand Variation
  - Effect of Parameter Variation
- Implications
Production Allocation Under Demand Variation

When demand ramps up, site usage increases significantly
Production Allocation Under Demand Variation

When demand ramps up, site usage increases significantly
Production Volume Under Demand Variation

Site A has the largest magnitude of fluctuation.
Production Allocation Under Parameter Variation

High Success Rate High Demand Capacity Utilization

SITE BASE SITE A SITE B SITE C SITE BASE SITE C

Massachusetts Institute of Technology
Production Allocation Under Parameter Variation

High Success Rate High Demand Capacity Utilization

Low Success Rate High Demand Capacity Utilization

2018 2019 2020 2021 2022 2023 2024 2025

Site A Base Site A Site B Base Site B Site C Base Site C

Full Target Minimum
Low Success Rate Puts Facilities at High Risk

Low Success Rate & High Demand

Capacity in Weeks

2018 2019 2020 2021 2022

Year

Full Capacity
Target Capacity
Minimum Capacity

Extra Capacity Needed

2023 2024 2025

5.12 1.84
The Riskiest Scenario – All Parameters at Low Level

Capacity Utilization under Low Manufacturing Performance & High Demand

Weeks

Full Capacity
Target Capacity
Minimum Capacity

All Sites Are Fully Utilized!

Site A Base  Site A  Site B Base  Site B  Site C Base  Site C

Year

2018  2019  2020  2021  2022  2023  2024  2025
The Riskiest Scenario

Extra Capacity Needed to Fulfill the Demand Requirement

Substantial Amount of Unmet Demand Every Year!

Opening a new capacity can cost $0.5 ~ 1 Billion USD
Parameter Sensitivity Analysis

None of the parameters are significantly different in regards to their capacity deviation from the base case scenario. In other words, no parameter is more sensitive than the others.

<table>
<thead>
<tr>
<th>Allocation Deviation from the Base Case under the Following Scenarios</th>
<th>P-Value (a = 5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low KGS Compared with Low RW</td>
<td>0.252 (&gt;0.025)</td>
</tr>
<tr>
<td>Low RW Compared with Low SR</td>
<td>0.824 (&lt;0.975)</td>
</tr>
<tr>
<td>Low KGS Compared with Low SR</td>
<td>0.744 (&lt;0.975)</td>
</tr>
</tbody>
</table>
Agenda

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The fluctuations of all three parameters – success rate, kilograms per run, and runs per week – impact the capacity utilization significantly.

XYZ Co. needs to pay attention to low production speed and low productivity under the high demand scenario as, in this scenario, all sites reach or surpass the target capacity level.

Optimization model is a holistic way to analyze the effect of several varying factors simultaneously.
Future Implications

- **Number of drugs:** the model can be extended by allocating multiple APIs simultaneously.

- **Scenario testing:** an on/off switch can be added to the model that specifies which regions can supply which market, and how would this affect capacity changes.

- **Market constraints:** regulatory compliance by production location can be incorporated into the model by giving a penalty amount for facilities without approval.
Thank You!  Questions?
Appendix: Model Formulation

Objective function:

\[
\text{Min } \sum_{M,T,API,DL,S} (XW^+_m,t,api,dl,s + XW^-_m,t,api,dl,s + U1 * P_{m,t,api,dl,s}) + U2 * \sum_{T,API,DL,S} (\text{ExtraThput}_{t,api,dl,s} + \text{SlackThput}_{t,api,dl,s})
\]

- **M**: set of manufacturing factories
- **T**: timeframe in years {2018...2025}
- **API**: active pharmaceutical ingredient
- **DL**: set of demand levels
- **S**: stochastic scenarios within each demand level

- **ThputM**: non-negative variable to capture manufacturing amount, in kilograms
- **SlackThput**: non-negative variable to capture manufacturing volume in case extra capacity is needed, in kilograms
- **ExtraThput**: non-negative variable to capture manufacturing volume in case total capacity does not reach the minimum capacity level, in kilograms
- **W**: non-negative variable to capture site capacity utilization measured in weeks
- **P**: binary variable showing whether or not a site is used (1=the site is used for production, 0=the site is not used for production)
- **XW+**: non-negative variable captures the excess of ‘Weeks+BaseUsage’ from target capacity
- **XW-**: non-negative variable captures the slack of ‘Weeks+BaseUsage’ from target capacity
Subject to:

**Constraint 1: Week capacity conversion constraint**

\[
W = \frac{\text{ThputM}_{m,t,api,dl} \cdot \text{SR}_{m,t,api,dl} \cdot \text{RW}_{m,t,api,dl} \cdot \text{KGS}_{m,t,api,dl}}{\forall m \in M, t \in T, api \in API, dl \in DL, s \in S}
\]

Capacity is measured in weeks through dividing the yearly production volume by the conversion factor --

runs per week multiplies kilograms per run multiplies success rate.

**Constraint 2: Throughput-Demand relation constraint**

\[
\sum_{M} \text{ThputM}_{m,t,api,dl} \pm \text{ExtraThput}_{t,api,dl,s} \mp \text{SlackThput}_{t,api,dl,s} = D_{m,t,api,dl,s}
\]

Demand constraint limits the annual production volume to be as close to the annual demand as possible. If total

\text{ThputM} -- production in kilograms -- exceeds demand, \text{ExtraThput} is positive; if it is under demand, \text{SlackThput} is positive.
**Constraint 3: Week capacity bounds**

Minimum Target Capacity \* \( P_{m,t,api,dl,s} \) \leq \( W_{m,t,api,dl,s} \) + \( \text{BaseUsage} \)

\( W_{m,t,api,dl,s} + \text{BaseUsage} \leq \text{Site Full Capacity} \* P_{m,t,api,dl,s} \)

(\text{where } P \text{ is functional when } \text{BaseUsage} = 0; \text{ i.e. if } W = 0 \& \text{BaseUsage} = 0, P = 0)

Upper capacity limit constraint: Site binary variable \( P \) is determined by capacity \( W \) and taken capacity \( \text{BaseUsage} \).

Only when \( W \) and \( \text{BaseUsage} \) are 0, \( P \) is 0.

Lower capacity bound: to make sure \( P \) is 1 if the sum of \( W_{m,t,api,dl,s} \) and \( \text{BaseUsage} \) is positive.
Constraint 4:

**Definition constraint for positive deviation from target capacity**

\[ W_{m,t,api,dl,s} - \text{Target Capacity} \leq XW^+_{m,t,api,dl} \quad \forall m \in M, t \in T, api \in API, dl \in DL \]

**Definition constraint for negative deviation from target capacity**

\[ \text{Target Capacity} - W_{m,t,api,dl,s} \leq XW^-_{m,t,api,dl} \quad \forall m \in M, t \in T, api \in API, dl \in DL \]
<table>
<thead>
<tr>
<th>Year</th>
<th>Low KGS Deviation from Base Case</th>
<th>Low RW Deviation from Base Case</th>
<th>Difference between Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>24%</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>2019</td>
<td>23%</td>
<td>30%</td>
<td>-7%</td>
</tr>
<tr>
<td>2020</td>
<td>14%</td>
<td>19%</td>
<td>-5%</td>
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<tr>
<td>2021</td>
<td>6%</td>
<td>5%</td>
<td>1%</td>
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<tr>
<td>2022</td>
<td>31%</td>
<td>10%</td>
<td>21%</td>
</tr>
<tr>
<td>2023</td>
<td>25%</td>
<td>28%</td>
<td>-4%</td>
</tr>
<tr>
<td>2024</td>
<td>12%</td>
<td>17%</td>
<td>-5%</td>
</tr>
<tr>
<td>2025</td>
<td>9%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Average</td>
<td>0.02</td>
<td>Standard Deviation</td>
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<tr>
<td>Standard Error</td>
<td>0.035</td>
<td>T Score</td>
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<tr>
<td>P Value (α=5%)</td>
<td>0.252 (&gt;0.025)</td>
<td>P Value (α=5%)</td>
<td>0.824 (&lt;0.975)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Low RW Deviation from Base Case</th>
<th>Low SR Deviation from Base Case</th>
<th>Difference between Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>11%</td>
<td>25%</td>
<td>-14%</td>
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<tr>
<td>2019</td>
<td>30%</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>2020</td>
<td>19%</td>
<td>11%</td>
<td>8%</td>
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<td>2021</td>
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<td>10%</td>
<td>25%</td>
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<tr>
<td>P Value (α=5%)</td>
<td>0.824 (&lt;0.975)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Allocation Decision Depends on Three Things

1. The product of three manufacturing parameters

2. The baseload of the production site

3. The target capacity level