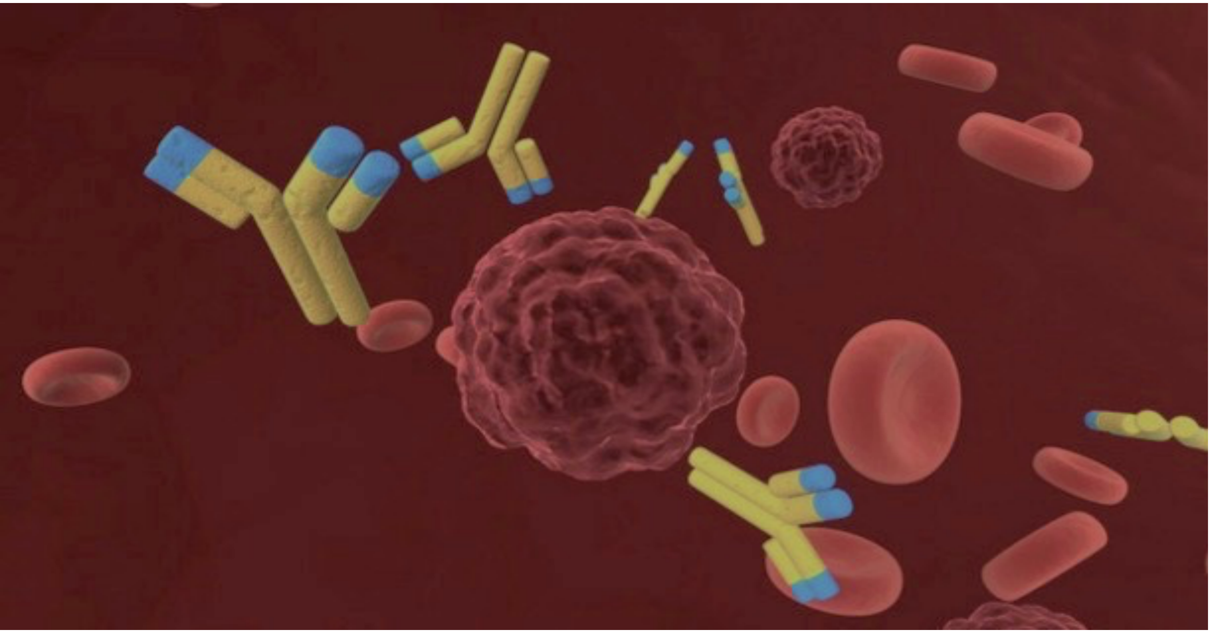

Strategic Capacity Planning for Biologics Under Demand and Supply Uncertainty

By Sifo Luo

05/25/2017

Thesis Advisor: Ozgu Turgut

Massachusetts Institute of Technology

Agenda

- Industry Background
- Problem Statement
- Optimization Model
- Results
- Implications

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- **Industry Background**
  - **Biologics and Long Range Planning**
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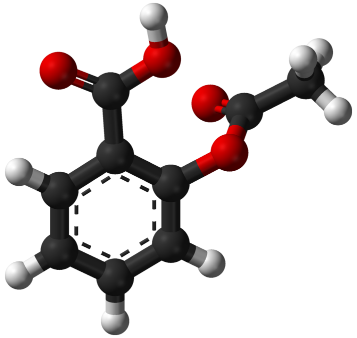
What Are Biological Products?

Small Molecule Drugs

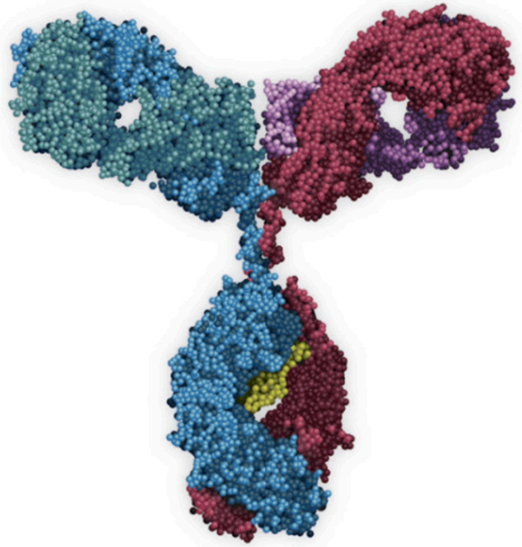
Organic or chemically synthesized, such as Aspirin



vs.

Big Molecule Products

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



Herceptin (breast cancer)

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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

Agenda

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- **Problem Statement**
  - **Capacity Planning in XYZ Co.**
  - **Research Question**
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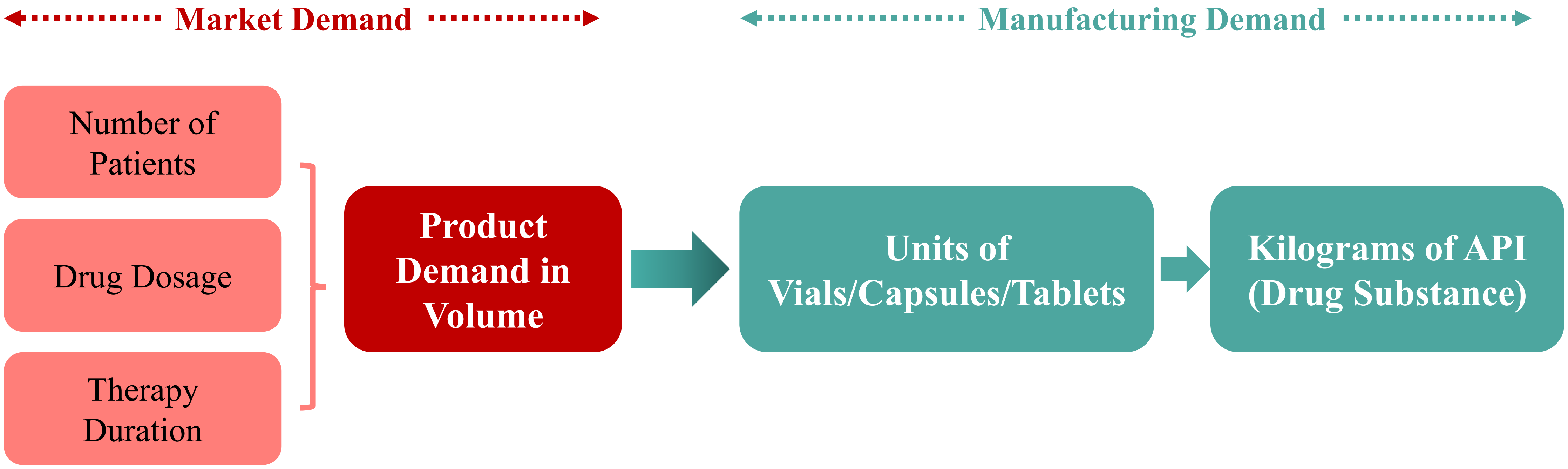
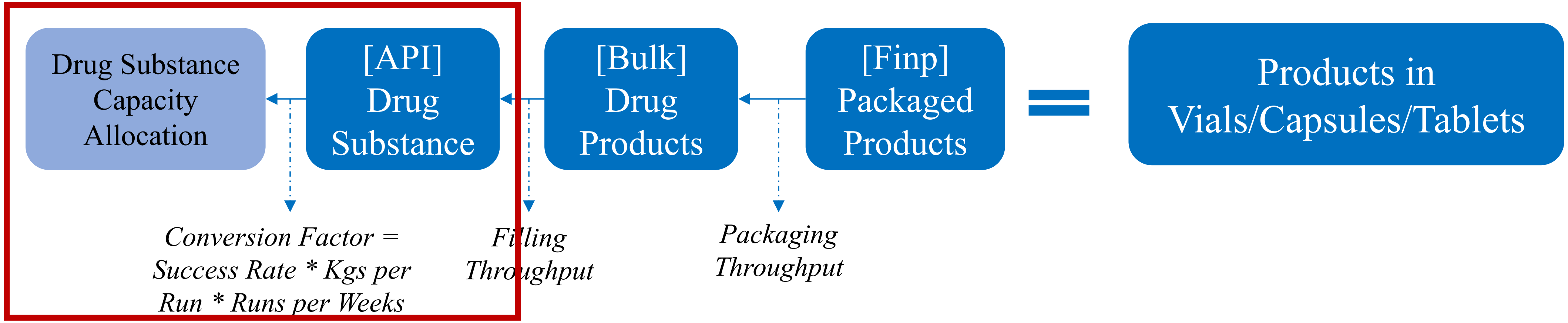
Demand Planning Drives Supply Planning



Current Capacity Planning Process in XYZ Co.

Simplified biologics supply chain

Capacity planning flow



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Three Manufacturing Performance Parameters

Success Rate (SR)

Expected ratio of runs (batches) that are successfully made

Kilograms per Run (KGS)

The average production volume expected from a batch

Runs per Week (RW)

How many batches the site can run

At XYZ Co., these parameters of the production facilities are kept at constant expected self-reported values in capacity planning

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
- 8 Future Years
- 3 Production Sites
- 3 Manufacturing Parameters

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

Scenario Category	Drug	API	2018	2019	2020	2021	2022	2023	2024	2025
Demand Basecase	Drug X	API 1	140.0	155.3	153.1	130.9	111.9	113.5	99.5	126.9
Demand Basecase	Drug X	API 1	223.1	246.8	280.9	288.3	270.5	279.5	248.1	343.8
Demand Basecase	Drug X	API 1	267.6	267.2	193.7	149.3	128.6	130.8	115.3	143.4
Base Scenario Annual Demand			**630.8**	**669.3**	**627.6**	**568.4**	**511.1**	**523.8**	**462.9**	**614.0**
Demand Downside	Drug X	API 1	93.3	137.0	107.1	80.1	67.2	61.9	59.7	29.3
Demand Downside	Drug X	API 1	193.6	203.4	214.8	198.6	176.0	179.5	157.1	216.5
Demand Downside	Drug X	API 1	230.8	212.4	145.9	107.4	87.9	86.8	75.5	93.2
Downside Scenario Annual Demand			**517.7**	**552.8**	**467.9**	**386.1**	**331.1**	**328.2**	**292.3**	**338.9**
Demand Upside	Drug X	API 1	185.0	175.0	166.8	178.8	151.2	133.8	103.3	161.0
Demand Upside	Drug X	API 1	251.2	295.2	366.2	414.4	422.7	446.3	396.1	550.1
Demand Upside	Drug X	API 1	309.1	337.1	278.5	255.7	256.2	279.1	245.1	303.9
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

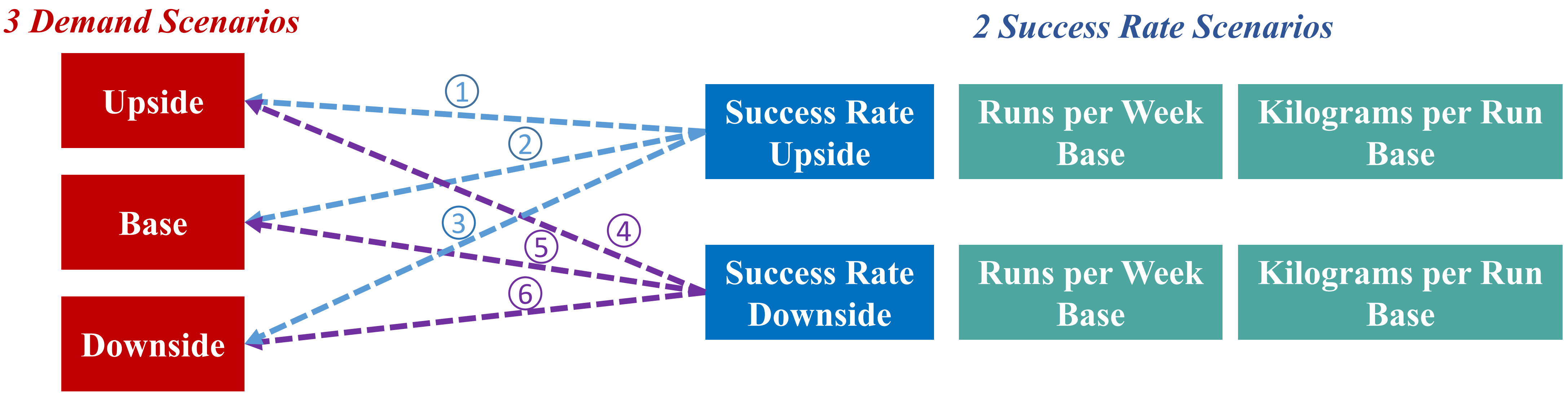
Optimization Model Parameters

- Manufacturing Parameters

Parameter Scenarios	Success Rate *(SR)*	Kilograms per Run *(KGS)*	Runs per Week *(RW)*
Upside Range		Base Case * (1 + 10%)	
Downside Range		Base Case * (1 – 30%)	

Scenario Schema

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

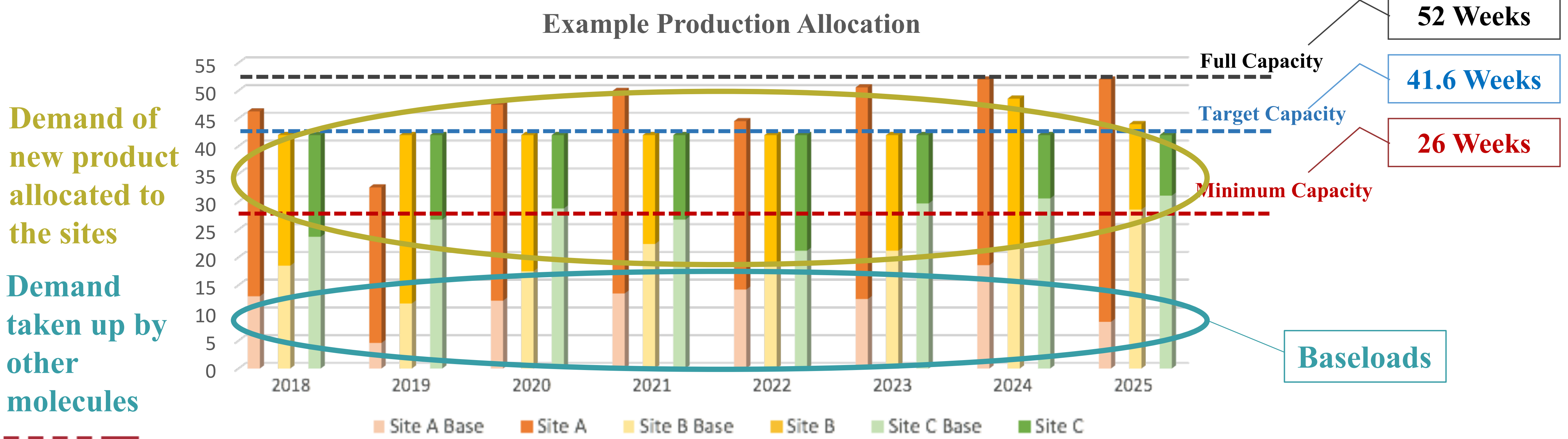


Example scenario generation process for *success rate*, while the other two parameters are kept at base values

Optimization Model Decision Variables

Production Capacity

Capacity of manufacturing facilities is measured in weeks.



Optimizing the Site Allocation and Selection

Objective Function:

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

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

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This Model is Subject to Three Main Constraints

Constraint 1: Capacity Conversion

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

(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

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- **Results**
  - **Effect of Demand Variation**
  - **Effect of Parameter Variation**
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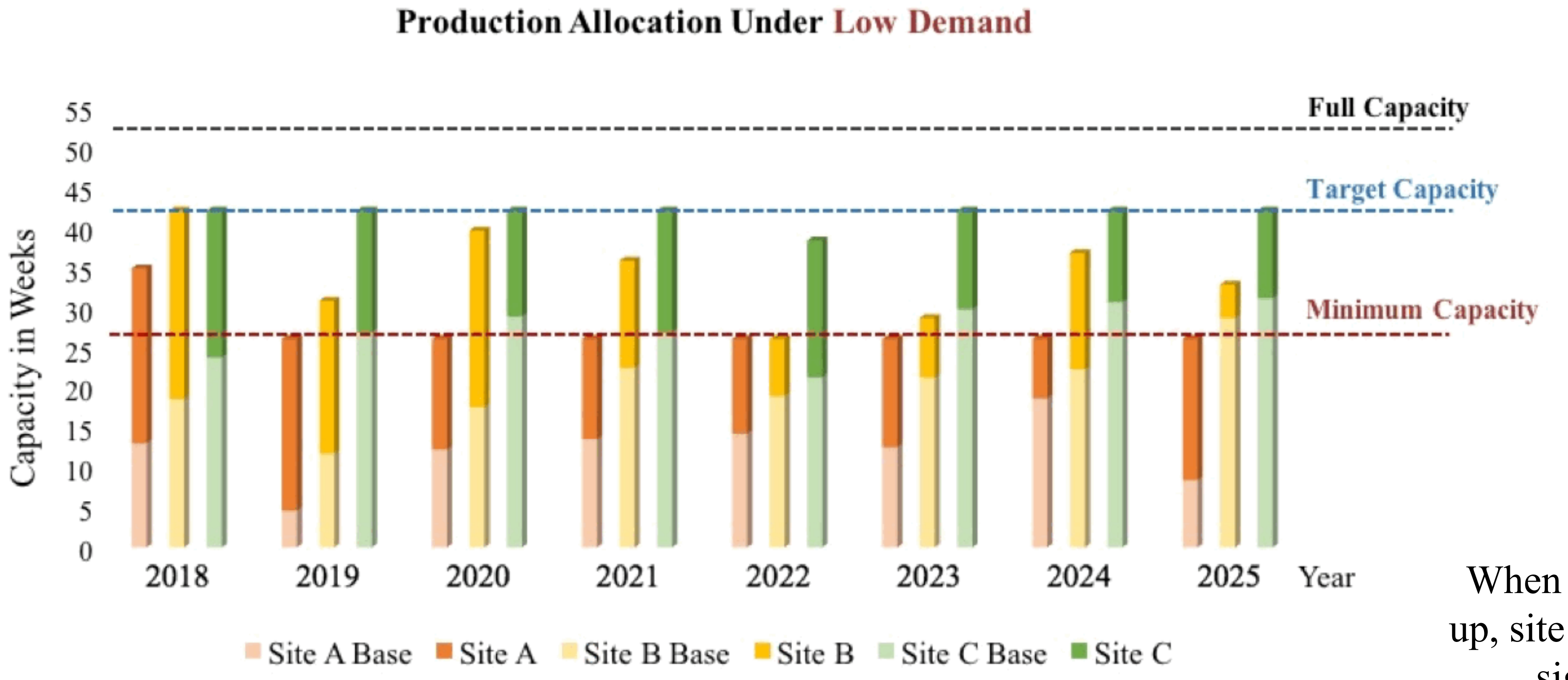
Production Allocation Under Demand Variation



When demand ramps up, site usage increases significantly

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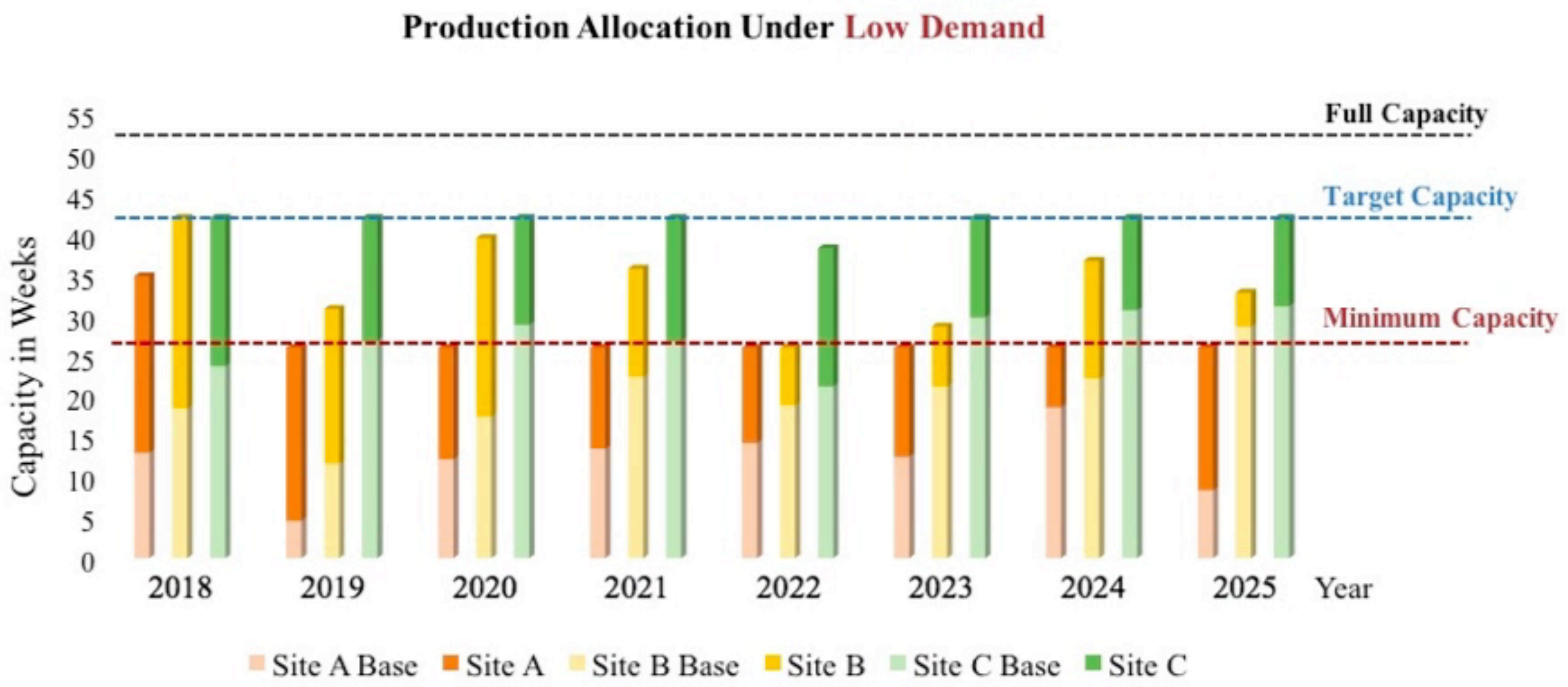
Production Allocation Under Demand Variation



When demand ramps up, site usage increases significantly

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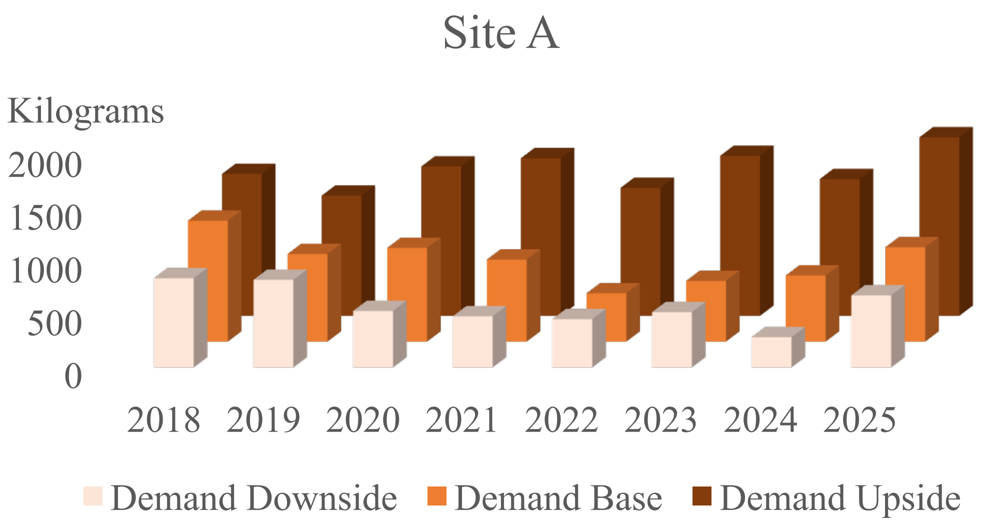
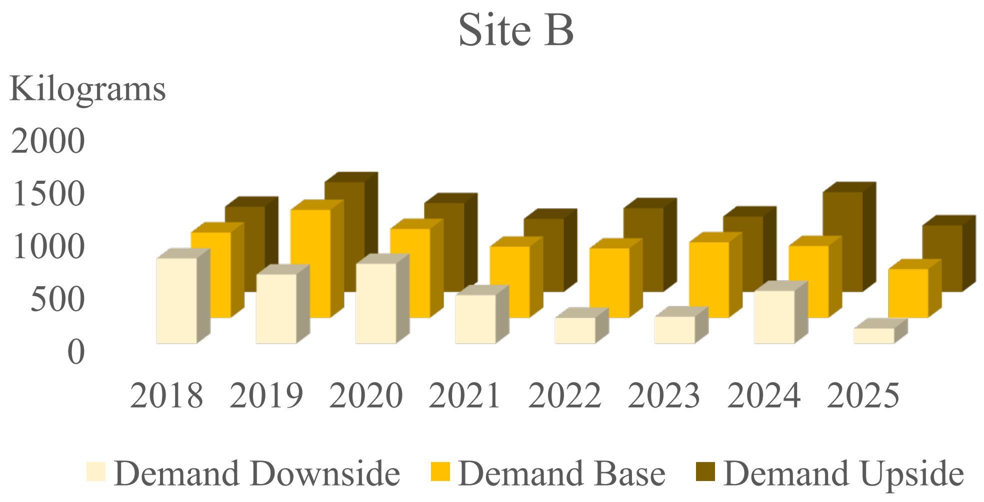
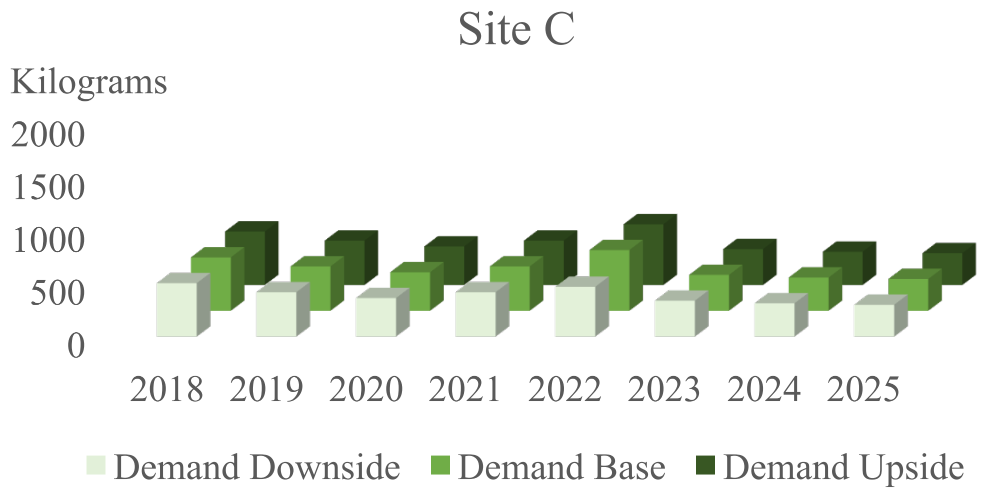
Production Volume Under Demand Variation





Site A has the largest magnitude of fluctuation



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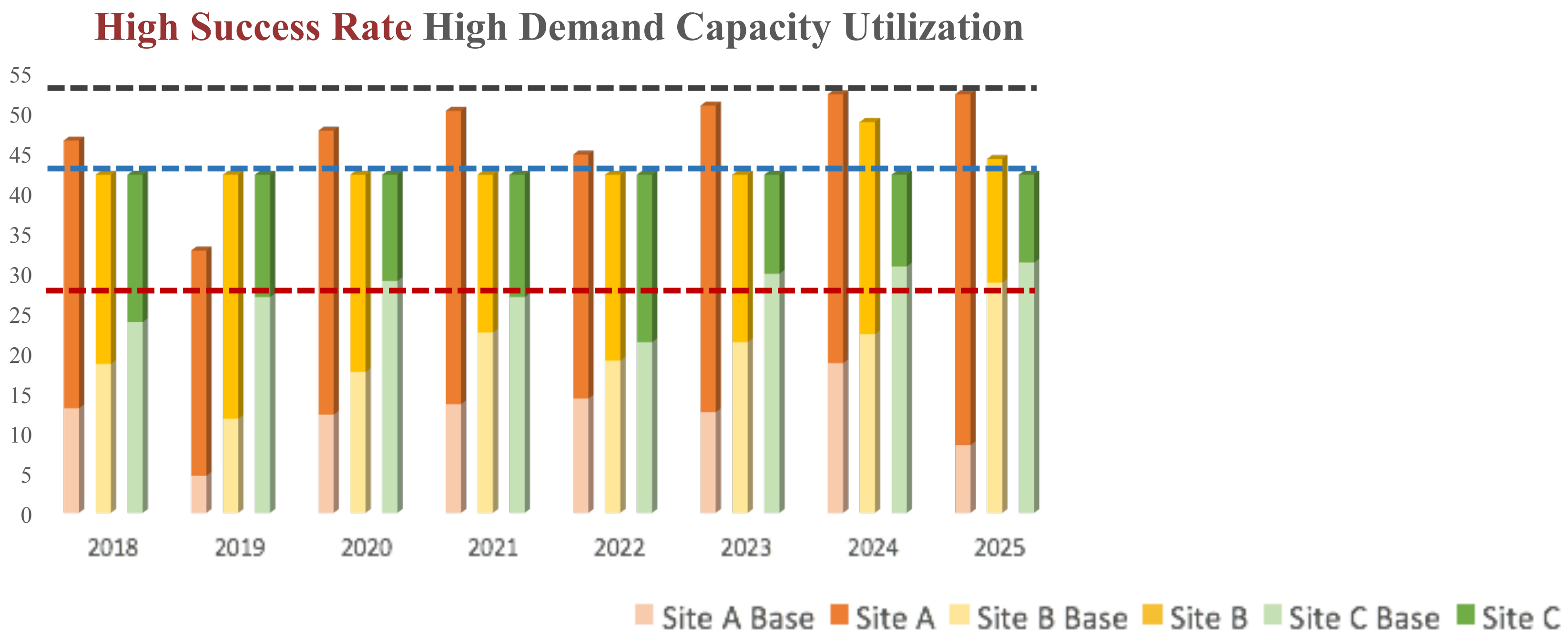
Production Allocation Under Parameter Variation



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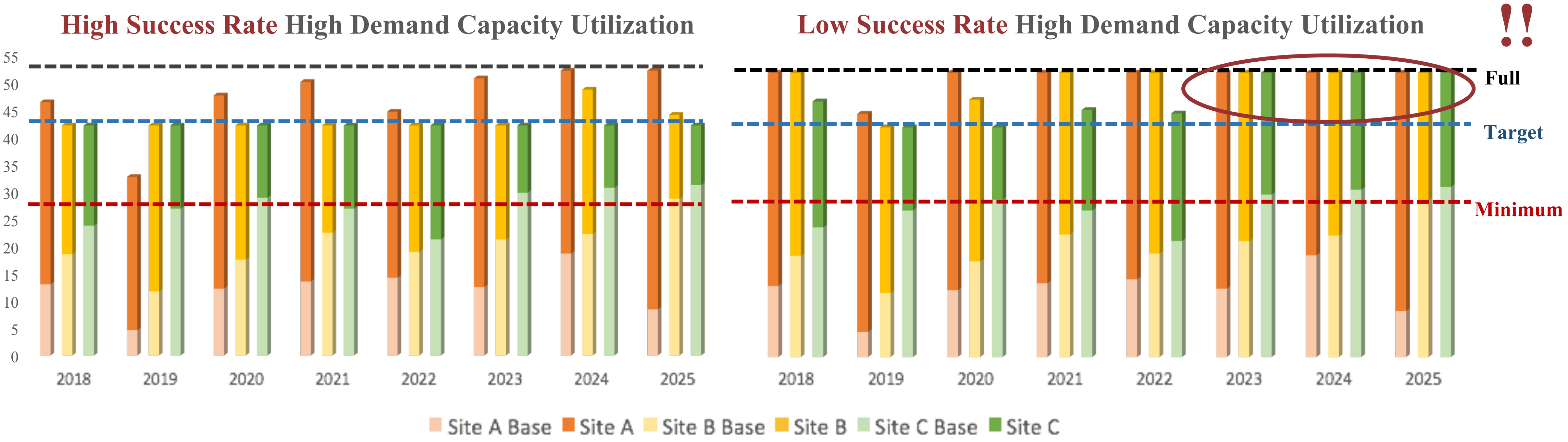
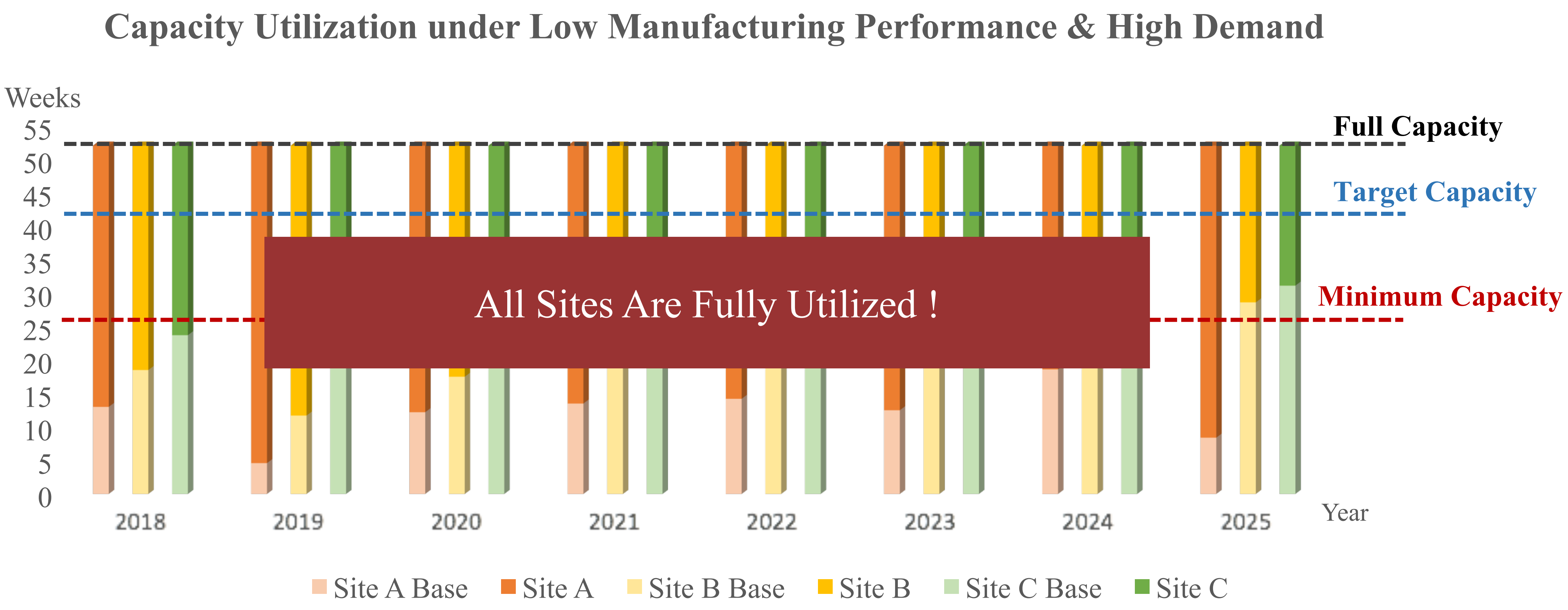
Production Allocation Under Parameter Variation



Low Success Rate Puts Facilities at High Risk

The Riskiest Scenario – All Parameters at Low Level



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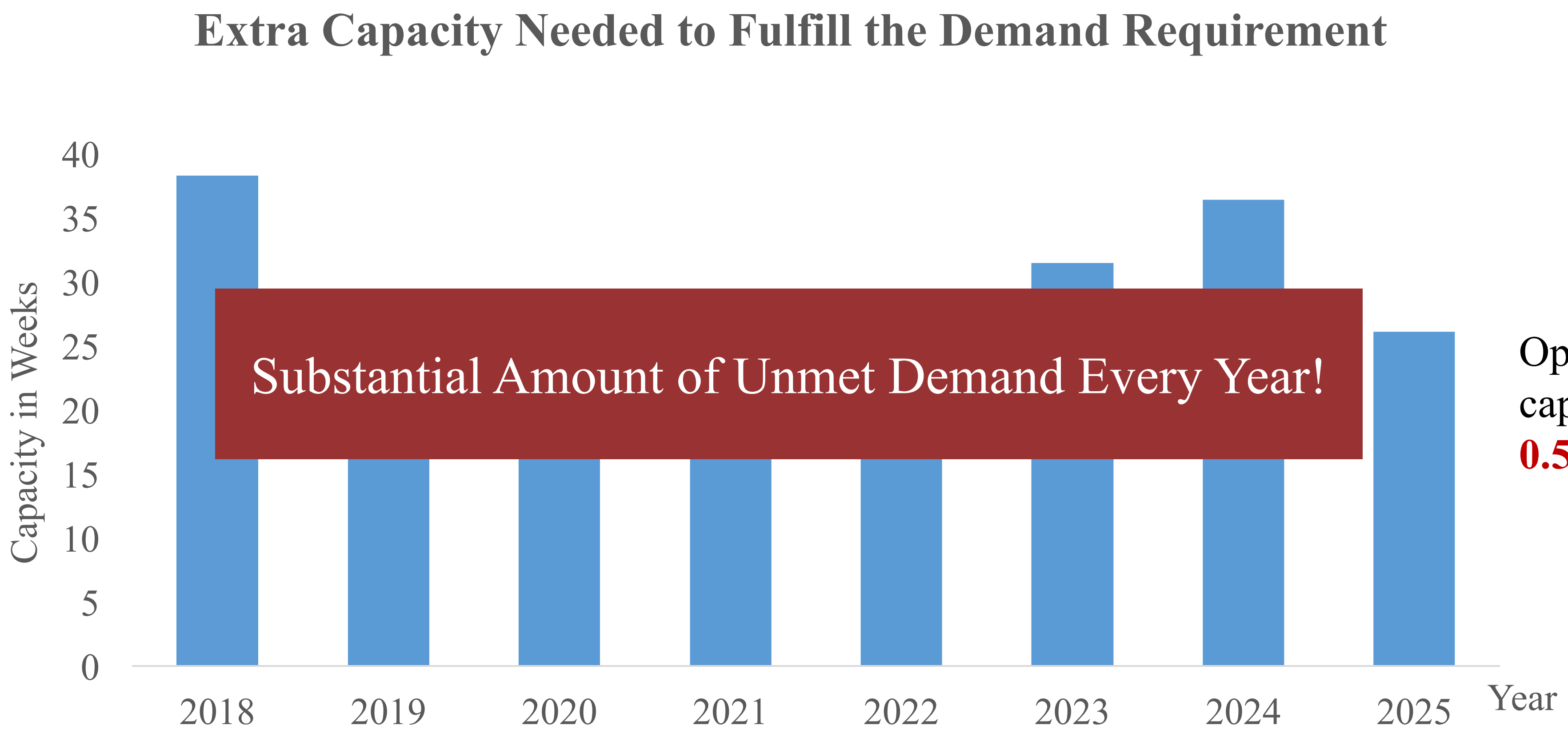
The Riskiest Scenario



Opening a new capacity can cost **0.5 ~ 1 Billion** USD

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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.

Allocation Deviation from the Base Case under the Following Scenarios	P-Value (a = 5%)
Low KGS Compared with Low RW	0.252 (>0.025)
Low RW Compared with Low SR	0.824 (<0.975)
Low KGS Compared with Low SR	0.744 (<0.975)

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Conclusion

- 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?

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Appendix: Model Formulation

Objective function:

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

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

$$W = \frac{ThputM_{(m,t,s,api,dl)}}{SR_{(m,t,s,api,dl)} * RW_{(m,t,s,api,dl)} * KGS_{(m,t,s,api,dl)}} \quad \forall m \in M, t \in T, api \in API, dl \in DL, s \in S$$

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

$$\sum_M ThputM_{m,t,api,dl} \pm ExtraThput_{t,api,dl,s} \mp SlackThput_{t,api,dl,s} = D_{m,t,api,dl,s}$$

Demand constraint limits the annual production volume to be as close to the annual demand as possible. If total *ThputM* -- production in kilograms -- exceeds demand, *ExtraThput* is positive; if it is under demand, *SlackThput* is positive.

Constraint 3: Week capacity bounds

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

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

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

Upper capacity limit constraint: Site binary variable *P* is determined by capacity *W* and taken capacity *BaseUsage*.

Only when *W* and *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 *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

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

Year	Low KGS Deviation from Base Case	Low RW Deviation from Base Case	Difference between Deviations
2018	24%	11%	13%
2019	23%	30%	-7%
2020	14%	19%	-5%
2021	6%	5%	1%
2022	31%	10%	21%
2023	25%	28%	-4%
2024	12%	17%	-5%
2025	9%	4%	6%
		Average	0.02
		Standard Deviation	0.10
		Standard Error	0.035
		T Score	0.703
		P Value (a=5%)	0.252 (>0.025)

Year	Low RW Deviation from Base Case	Low SR Deviation from Base Case	Difference between Deviations
2018	11%	25%	-14%
2019	30%	14%	16%
2020	19%	11%	8%
2021	5%	17%	-12%
2022	10%	25%	-15%
2023	28%	28%	0%
2024	17%	17%	0%
2025	4%	21%	-17%
		Average	-0.04
		Standard Deviation	0.12
		Standard Error	0.043
		T Score	-0.996
		P Value (a=5%)	0.824 (<0.975)

Year	Low KGS Deviation from Base Case	Low SR Deviation from Base Case	Difference between Deviations
2018	24%	25%	-1%
2019	23%	14%	9%
2020	14%	11%	3%
2021	6%	17%	-11%
2022	31%	25%	5%
2023	25%	28%	-4%
2024	12%	17%	-5%
2025	9%	21%	-11%
		Average	-0.02
		Standard Deviation	0.07
		Standard Error	0.026
		T Score	-0.689
		P Value (a=5%)	0.744 (<0.975)

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