Flexibility in a Biotech Manufacturing Facility: An Options Analysis for Monoclonal Antibody Production

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EXECUTIVE SUMMARY

This assessment was completed to analyze the application of flexibility in the design of biotech manufacturing facilities. For the purposes of the analysis, the therapeutic for NPV analysis was based on available data for Avastin, the blockbuster oncology therapy manufactured and marketed by Genentech (now owned by Roche AG). A Monte Carlo simulation was completed based on estimated market demand growth rates over the 20-year horizon for three distinct designs as follows:

1. Fixed Design:
   A traditional biotech facility setup where capacity was maximized initially with no additional need for modifications
2. Standard Flexible Design:
   A facility that was initially built with less capacity, but the capital investment was lower. However, it could support additional bioreactor trains as market demand increased.
3. Future Flexible Design:
   A facility utilizing single-use disposable bioreactor technology in lieu of traditional stainless steel construction and having the lowest capital investment of all options. On the other hand, raw material costs were higher due to the need for new bioreactors for each production run.

The design lever for the flexible designs was the addition of bioreactor trains to increase production capacity. Additional bioreactor trains were added in the following year when market demand was greater than 80% of total plant capacity (i.e. decision factor = 80%) in the previous year. The analysis clearly showed that the Fixed Design had a lower mean ENPV compared to the flexible designs. For the flexible designs analyzed, the Future Flexible Design had a higher ENPV in 99.91% of all simulation trials. The sensitivity analysis also showed that the Future Flexible Design was favored in a majority of the situations as the decision factor varied from 50% to 150%. The optimal decision factor (i.e. the factor leading to the highest ENPV) was 80% for the Future Flexible Design and 90% for the Standard Flexible Design. The analysis proves that single-use disposable technology is not cost efficient when product demand is extremely high, since using a large number of disposable bioreactors has a significant impact on

operating costs.

TABLE OF CONTENTS

INTRODUCTION

There is no question that manufacturing technology in the biotech industry is changing. In the beginning, most companies used a “buckets and hose” approach – the processes were manual and the production yields were quite low. As the technology matured, the production processes were better understood, and the yields have increased 5 to 10 fold (depending on the process). Consequently, many companies now have excess capacity. Some companies, especially traditional pharmaceutical ones, are cannot fill this capacity with new therapeutics since their R&D groups are struggling to find and develop candidates.

Several biotech companies have developed a number of monoclonal antibodies (mAbs) that are being tested in clinical trials or are already available commercially. Monoclonal antibodies are proteins that attack or neutralize a specific virus or bacteria in the body. By 2016, monoclonal antibodies could represent 11 of the top 50 best-selling therapeutics, including 6 of the top 10 products (1). Patients require large dosages for maximum effectiveness. Companies must therefore produce high volumes of the product. Due to competition and regulations, however, it is very difficult to determine what capacities are needed for production. Moreover, companies need to allow at least 2-3 years for construction and validation of a new facility.

As part of this assessment, we will examine how flexibility can be applied in the construction of a biotech manufacturing facility.The facility produces a single oncology therapeutic, which is based on a currently available therapy, and the time horizon for manufacturing and marketing is 20 years. In this case, market demand over the time horizon was uncertain. Three facility designs were analyzed – a traditional fixed facility, a traditional facility with expansion capability, and a new-age facility with expansion capability. In both flexible designs, the expansion capability (i.e. system design lever) was the addition of bioreactor trains that would increase product output at the facility. Cost models were created for each design type, and simulations were conducted with

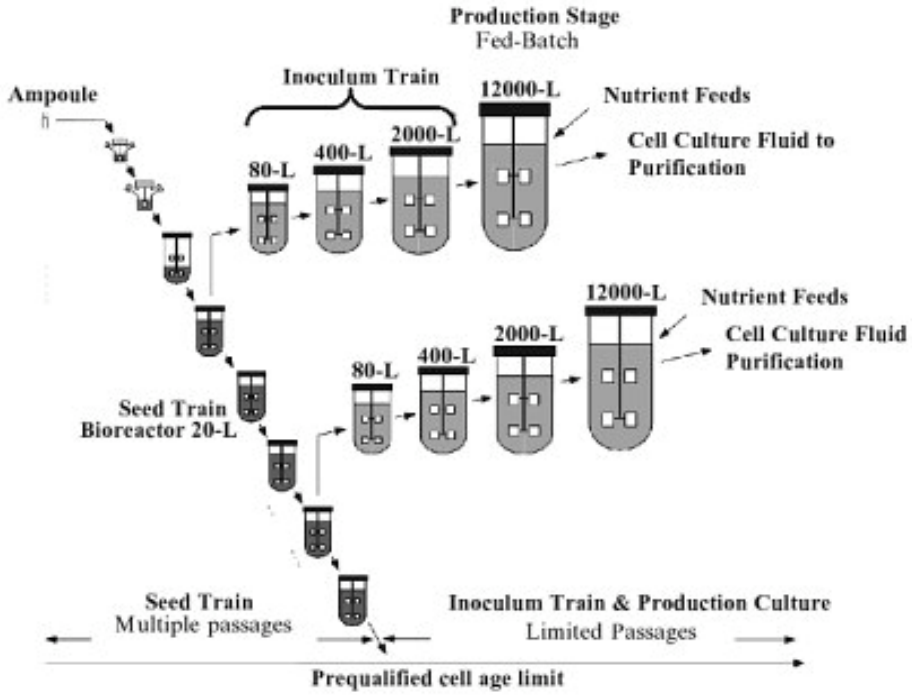
varying demand growth rates. A sensitivity analysis was also completed for the decision rule to examine the effects of exercising various decision factors.

SYSTEM DESIGN

Background

Biotech manufacturing facilities are designed to support various unit operations that can be placed into two categories – upstream production processes and downstream production processes. Both the upstream and downstream processes are developed very early in the drug development process. Any process changes made once the drug is used in late-stage trials or is available commercially require regulatory approval and additional testing to ensure product quality is not compromised. The upstream production processes involve scale-up of genetically modified cells/bacteria, which produce the needed protein, from vials to large-scale production bioreactors. The scale-up process can take anywhere from 1 to 4 weeks, with microbial scale-ups being far faster than cell culture scale-ups. it requires different-sized flasks and bioreactors at various steps. The following is a diagram of a typicalcell culture scale-up implemented in a biotech manufacturing facility (2):

Fig. 1. Example of a Cell Culture Scale-Up



The set of bioreactors used in the scale-up process is known as the bioreactor train. The bioreactor sizes for scale-up will vary depending on what the Process Development Group finds to be the most efficient combination. In most cases, scale-up starts at 20L - 100L, shifting to a 300L - 500L, then to a 1000L - 2000L, and then the final-stage bioreactor. Final-stage bioreactors can be as large as 25,000L, but a bioreactor that large would require another scale-up step prior to exposure. The objective for process development is to determine the most efficient process that results in the highest titer (grams of protein produced per Liter). While 3 -5 g/L is the industry standard, some of the newest processes developed within the last two could years reach 10 – 15 g/L (3). Since such processes are not widely implemented at this time, the analysis considered the 3-5 g/L range for the application.

The downstream processes involve recovering protein produced in the media (i.e. broth) through various unit operations such as centrifugation and chromatography. Downstream operations only take up to 3 days to complete, which is much faster than the upstream production processes. Therefore, manufacturing plants generally do not need additional downstream equipment (e.g. chromatography columns, homogenizers, etc.) to accommodate increased capacities. The combined efficiency of the protein recovery and purification steps can range from 70% to 80% (4). The final solution

containing the protein, also known as the bulk drug substance, then undergoes formulation, fill/finish, and packaging steps to prepare the product for patient use. This analysis will not account for such steps, as there are no levers to increase protein output in these unit operations. However, those costs are accounted for in the NPV analysis.

There are various ways for a manufacturing plant to increase output. Looking at this from the perspective of applying a design lever, the preferred way to increase output would be to add additional bioreactor trains. As previously mentioned, any process changes require rigorous testing and potentially clinical trials; the cost would be in the hundreds of millions, depending on how much testing the regulatory agencies requires. Moreover, the time requirement could stop production for several months. It is therefore more cost-effective to install additional bioreactor trains rather than making process changes.

Monoclonal Antibody Production for Analysis

The data used for this analysis comes from general research on mAb production. Since most of the information is proprietary, the data set was adjusted for the purposes of this project. The drug in questions was fabricated for this assessment, but the data for analysis was based on scenarios predicted for Avastin, a monoclonal antibody manufactured and marketed by Genentech (now owned by Roche AG), in 2009. A biotech company received approval for their new oncology therapeutic, “Nishumab”. While the drug was initially approved for one type of cancer (e.g. colorectal), further clinical trials to determine effectiveness with other cancers (lung, head & neck, breast, etc.) were being conducted. If further indications are approved, demand and total revenue will increase over time; this is in addition to the number of patients taking the drug for already-approved indications. However, after 10 years, biosimilars (i.e. generic biologic therapeutics) could enter the market, and the demand growth rate will decrease. Exclusivity for biologics has not been well defined as compared to other small-molecule drugs because there is currently no pathway for the approval for generic biologics in the U.S. Consequently, 10 years is a conservative estimate for such exclusivity. After a certain amount of time (i.e. 20 years), a new therapeutic will become the drug of choice and the market share will essentially become 0%. The manufacturing facility will be

salvaged for any remaining value., and the company will potentially work to develop another molecule.

Similar to Avastin, Nishumab is seen as “the next big thing”, and manufacturing has to plan accordingly for demand increases over time. The biotech company producing Nishumab must choose the appropriate capacity to meet demand for each year. For several high-profile products, biotech companies initially constructed their facilities assuming market demand would be sustained or that another product could be transferred in to take its place.In many situations when building a facility, initial construction and design plans are already made prior to receiving regulatory approval.The analysis was done under the assumption that Nishumab met all endpoints in the final Phase III trial and would receive approval from regulatory agencies. To determine the best production plan for the therapeutic, all costs must be accounted for. As a result, the NPV model must account for expenses that are not manufacturing-related in addition to those that are. In all cases, the following were assumed and accounted for in the NPV cost models:

- In order to maintain simplicity, the biotech company will only produce Nishumab. In reality, a biotech company would use revenue to fund the development of other therapies for revenue growth. However, this would lead to a very complex cost model and would take away from the true examination of manufacturing costs.
- Fill/Finish and Packaging would be done by a contractor at a set rate (per gram)
- Inventory held would match the year’s demand to ensure product supply in case of an emergency.
- R&D and SG&A expenses were a constant percentage of revenues for each year. In a real-world situation, companies could alter these percentages to boost operating incomeor .
- Nishumab revenue is $2,000/g, which is modest in comparison to the revenues per gram for other monoclonal antibodies (5).

Market Demand Uncertainty& Distribution Characteristics

Biotech manufacturing facilities, like all manufacturing facilities, are built to meet market demand in order to maximize revenue. One of the major issues when deciding on capacity is the market demand for the therapeutic. It is primarily exogenous, meaning that the manufacturing plant does not have an impact on demand. The only exception to this is the rare case when product quality is affected in a released lot. Although it is uncommon, there are product re-calls when a company detects foreign objects or substances in their released therapies. There are a variety of reasons for demand growth of a specific therapeutic. The following is a list of the factors that can increase market demand:

- Regulatory approval for other indications
- Issues with competing products
- Increases in diagnosis (note: can be tied to aging populations)

On the other hand, there are unforeseen actions that can decrease market demand for the therapeutic. The following includes some of the major factors:

- Competing therapeutics (both small-molecule and protein-based)
- Regulatory approval changes
- Manufacturing setbacks (e.g. recalls, contaminations, etc.)

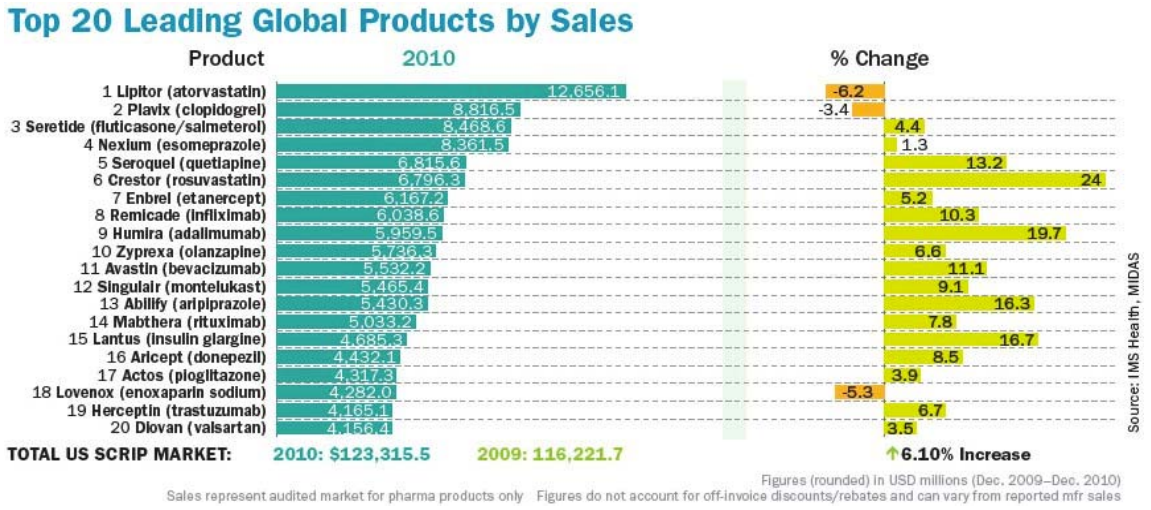
Another factor that must be considered is the potential for generic competition. Although there is currently no pathway for the approval of biosimilars, many experts believe that one will be established in the near future. Demand for name-brand biotech therapeutics will decrease with such competition. However, due to the higher costs with manufacturing biotech drugs and the fact that the proteins produced are not identical, market share may not be completely overtaken.

The initial demand for Nishumab is anticipated to be 1,000,000 g, which is the current demand for Avastin with its multiple oncology indications. For the purposes of this assessment, demand growth (CAGR measurements) for the first 10 years and the second 10 years are different to represent a potential patent cliff (i.e. introduction of biosimilars in the market). The following table shows the values for both periods:

	Mean	Standard Deviation
First 10 Years	6.5%	5.0%
Last 10 Years	2.0%	2.0%

These values, which are normally distributed, were derived from current researchand modified for the purposes of this project (6). Looking at extreme CAGR values (i.e. 3 standard deviations), it is possible to have demand growth as high 21.5% and as low as -9.5%. This is reflective of real-world scenarios for commercial therapeutics. The following chart shows drug sales in 2010 for the top 20 pharmaceutical therapies (7):

Fig. 2. Global Sales for the Top 20 Therapies in 2010



Though this also includes small-molecule drugs as well, it illustrates how market demand varies in the industry. With regards to the mean and standard deviation for the last 10 years, the extreme CAGR values are also applicable. For example, erythropoietin-stimulating agents (ESAs) are a class of biotech therapies with expired patents. Sales for these products decreased by 3.17% in 2010 (7). Thus, extreme CAGR values are possible for a therapy such asNishumab.

Fixed Design

The fixed design would be employed for the following reasons:

- To accommodate long-term market demand without additional major capital investments later on
- To eliminate production downtime required with a major expansion
- To provide additional capacity in the case that a bioreactor train is down for maintenance

For this project, the fixed design was based on the biotech manufacturing facility used in the production of Avastin by Genentech in Oceanside, CA. The facility was modeled with the following features:

- 6 bioreactor trains with final bioreactor size of 15,000L (90,000L total capacity) will be used
- All bioreactors and downstream equipment are constructed from stainless steel (cleaning and sterilization required for each production run)
- Each bioreactor train can accommodate 20 batches per year

The product titer is 5 g/L, and product recovery is 1-2 days with a 75% yield. These are in line with typical monoclonal antibody production results as discussed in the previous section.

Standard Flexible Design

The standard flexible design employs most of the same features of the fixed design. However, instead of building 6 bioreactor trains initially, the facility only includes 2 bioreactor trains (final bioreactor size of 15,000L; 30,000L total capacity). However, the facility will be built to accommodate 4 additional bioreactor trains if market demand requires additional capacity. Product titer and recovery will remain 5 g/L and 75% respectively, since no process changes are being applied.

Future Flexible Design

The future flexible design represents a departure from a traditional biotech manufacturing facility. Instead of installing stainless steel bioreactors, which require cleaning and sterilization between production runs, the facility uses single-use, disposable bioreactors (three-layer plastic), which can be discarded after production runs. The initial capital investment is almost half that of a facility with full stainless steel equipment. However, the final bioreactor size is far smaller due to limitations with the disposable bioreactors. This facility, consequently, has far more bioreactor trains to match the output needed to meet demand. The facility has the following features:

- 15 bioreactor trains with final bioreactor sized of 2,000L (30,000L total capacity) will be used initially
- 5 additional bioreactor trains (10,000L capacity total) can be added to meet increasing demand
- Downstream equipment is constructed from stainless steel, like the fixed design
- Each bioreactor train can accommodate 20 batches per year

Annual costs for disposable bioreactors lead to increased raw material costs for this design. The expansion capabilities of the Future Flexible Design are less than those of the Standard Flexible Design (i.e. 10,000L versus 15,000L) because of the constraints on the supplier to provide the number of disposable bioreactors required (i.e. the supplier would not be able to increase the supply of disposable bioreactors so easily). Moreover, it is difficult to use a variety of disposable bioreactors due to testing and validation constraints. Therefore, there would be sourcing constraints. While 10,000L would be suitable in most cases, there may be some extreme cases where having the additional expansion capabilities would be more beneficial. This reflects a major issue when using single-use disposable bioreactors – a reliance on suppliers for the necessary equipment (single-source in most cases).

Like the previous designs, product titer and yield were assumed to be 5 g/L and 75%. Research suggests that product titers in disposable bioreactors are generally not as high

as those in stainless steel. However, given that titer can be in excess of 10 g/L for both types of bioreactors, it is very possible to achieve a product titer of 5 g/L in a disposable bioreactor these days.

SIMULATION METHOD

Background

For this analysis, Monte Carlo simulations (10,000 trials each) were carried out to determine the range of expected Net Present Values (ENPVs) with varying market demand CAGRs. The simulation and analysis were carried out using @Risk and Microsoft Excel.

The analysis performed looked at various statistics including the following: mean, standard deviation, P_5, P_{95}, minimum, and maximum. The Value at Risk-Gain (VARG) curve was also examined, as well as the number of times a particular design was favored (i.e. highest ENPV for the CAGR values generated to represent the first and last 10 years) for the simulations conducted. In this case, a benefit-cost ratio would not be entirely appropriate. The assumption made was that Nishumab had already received FDA approval, and so drug development costs were not accounted for. To understand the true project NPV, the drug discovery and development costs need to be accounted for. These costs are typically in excess of $1B and, depending on the number of projects undertaken prior to a successful project, could be much higher. Analyzing drug development costs for such a product would require extensive expertise in the oncology market and clinical development costs.

Decision Rule

In this analysis, the decision to expand capacity was based on comparing market demand and plant capacity.The decision factor is the percentage at which demand exceeds plant capacity in order to expand. For the initial analysis, if product demand is greater than 80% of plant capacity (i.e. 80% is the decision factor) in the previous year, the following was executed for the flexible designs:

1. For the Standard Flexible Design, 1 additional bioreactor train was installed to increase capacity. The additional trains would come online in the next year.
2. For the Future Flexible Design, 5 additional bioreactor trains (single-use disposable technology) were installed. The additional trains would come online in the next year.

This ensures product supply, such that every patient has access to treatment. If the decision rule were simplified to the extent that additional capacity was added only when demand exceeded capacity by at least 100%, there is a chance that patients would not have access to drug product. Consequently, the 80% margin is more likely to be applied in a real-world scenario.Appendix A includes the Excel formula applied to enforce the decision rule. In the sensitivity analysis (discussed below), we will examine how the expected NPV changes as the decision factor changes.

Sensitivity Analysis

Although a decision factor of 80% was selected for the primary decision rule, it is useful to examine how the decision factor can affect the expected NPV for each of the facility designs. While it is not recommended that a company not meet all demand for the purposes of treatment, it may be forced to delay expansions for a variety of reasons (e.g. automation updates, cash flow issues, etc.). The sensitivity analysis was completed for decision factors ranging from 50% to 150%. The mean ENPVs as well as the percentage of highest NPVs for the simulations were then assessed.

Cost Models

Each facility design had different costs based on what was required for that operation. For example, the facilities that used a flexible design hada lower number of employees at the beginning. However, the employee count grew when additional bioreactor trains were added to increase capacity. Inflation was accounted for with all operating costs (except depreciation) and facility expansions, since costs were expected to increase over the 20-year horizon. Depreciation was assumed to be a 20-year linear decrease and accounted for all facility expansions as well. The following table shows the costs associate with each design for this analysis:

		Fixed Facility	Standard Flexible Facility	Future Flexible Facility
Time Horizon	years	20	20	20
Discount Rate	%	10%	10%	10%
Initial Demand	g	1,000,000	1,000,000	1,000,000
Revenue	$/g	2,000	2,000	2,000
Capital Investment				
Initial	$	500,000,000	300,000,000	200,000,000
Additional	$/train	-	75,000,000	5,000,000
Operating Costs				
Depreciation (initial)	$	25,000,000	15,000,000	10,000,000
Raw Materials	$/g	10	10	20
Labor	$/person	150,000	150,000	150,000
Maintenance & Projects	$	5,000,000	7,500,000	300,000
Formulation/Fill/Finish/ Packaging & Distribution	$/g	80.00	80.00	80.00
Inventory	$/g	100.00	100.00	100.00
SG&A Expenses	% revenue	30%	30%	30%
R&D Expenses	% revenue	20%	20%	20%
Capacity				
Initial # of trains		6	2	15
Final Bioreactor Size		15,000	15,000	2,000
Batches Per Train	1 year	20	20	20
Titer	g/L	5	5	5
Yield	%	75%	75%	75%
Maximum number of trains		6	6	45
Additional trains added		0	1	5

Employment				
Initial # of employees		300	120	120
Additional employees	per train	0	45	6
Inflation (applied after first year)	%	3%	3%	3%
Decision Rule (when to add trains)	%	80%	80%	80%

Appendix A includes screenshots of the Excel files that were used to complete this analysis as well as information regarding the decision function. To calculate the net income for each year (*i*), the following equation was applied:

$$[Net\ Income]_i = [Revenue]_i + [Salvage\ Value]_i - [[SG\&A\ Expenses]_i + [R\&D\ Expenses]_i -$$
]

The Salvage Value was only applied at the end of the final year (*i* = 20). Much of this data was taken from current research in monoclonal antibody production (3,9). For the Net Present Value, the following equation was applied:

$$NPV = \sum_{t=1}^{20} \frac{Net\ Income_t}{(1+r)^t}$$

Based on research for discount rates in the pharmaceutical and biotech industries, the typical discount rate is 10% for these calculations (6). One line item that was not accounted for was taxes. This is because the manufacturing taxes are dependent on the production locations and what process is being carried. For this reason, it was excluded from the analysis. In addition, from our model, costs associated with manufacturing and supply were approximately 15% of revenue, which are in line with current estimates for typical biotech companies (8).

RESULTS AND ANALYSIS

Deterministic Results

The following results were obtained for the facility designs with the forecasted mean CAGR values for the first and last 10 years:

	Fixed Facility	Standard Flexible Facility	Future Flexible Facility
NPV	$7,963,664,258.17	$8,581,356,739.23	$8,754,940,378.24

Based on these results, the Future FlexibleDesign was expected to have a higher NPV, assuming that there was no fluctuation in market demand. However, since this is never the case, a simulation is more appropriate to determine how the NPVs will vary with various demand CAGRs for the first and last 10 years.

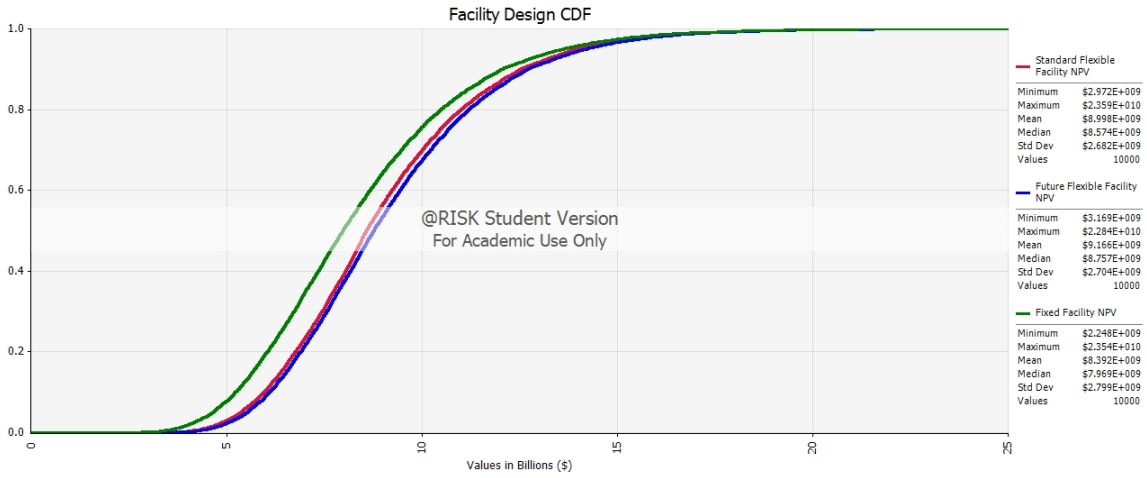
Simulation Analysis

The following results were found after conducting the 10,000-trial Monte Carlo simulation (decision factor = 80%):

	Fixed Design	Standard Flexible Design	Future Flexible Design
Mean ENPV	$8,391,950,000.00	$8,998,303,000.00	$9,165,863,000.00
Standard Deviation	$2,798,677,000.00	$2,681,876,000.00	$2,704,029,000.00
Minimum	$2,248,373,000.00	$2,972,429,000.00	$3,168,993,000.00
Maximum	$23,541,420,000.00	$23,588,710,000.00	$22,842,500,000.00
P_5	$4,631,118,000.00	$5,355,173,000.00	$5,509,338,000.00
P_{95}	$13,619,440,000.00	$13,971,700,000.00	$14,208,500,000.00

The following Value At Risk-Gain (VARG) curve was also determined:

Fig. 3. VARG Curve for the Simulation

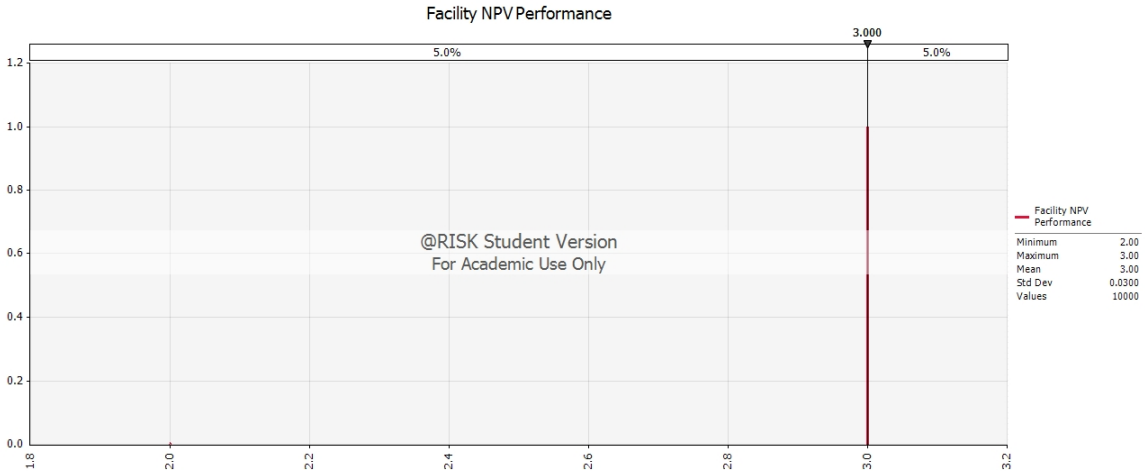


The flexible designs outperformed the fixed design is every category except for one (maximum ENPV for the Future Flexible Design). The beneficial ENPV increase with the flexible designs is 7.23% and 9.22% for the Standard Flexible and Future Flexible Designs respectively (difference in mean ENPV divided by Fixed Design ENPV). The Fixed Design had higher maintenance and project costs than either of the flexible designs, since the staff would be required to maintain six bioreactor trains for the time horizon; the flexible designs generally had less bioreactor trains that needed to be maintained. Consequently, the Operating Costs for the Fixed Design were greater, and the resulting ENPVs were less. Looking at the flexible designs, the Future Flexible Design outperformed the Standard Flexible Design in each of the same categories. Based on this analysis, the Future Flexible Design would be the design of choice for Nishumab.

The reason that the maximum NPV was greater for the Standard Flexible and Fixed Designscompared to the Future Flexible Designwas due to the expansion capabilities and raw material costs. The Future Flexible Design did not increase output at the same rate at the Standard Flexible Facility(i.e. 10,000L versus 15,000L capacity per incremental expansion) because of the supplier constraints in supplying the number of disposable bioreactorsthat would be needed to match the output of a 15,000L stainless-steel bioreactor. Furthermore, the total raw material costs for the Future Flexible Facility are significantly higher when the demand CAGRs are extremely high (e.g. > 3 standard deviations). However, the likelihood of this scenario happening is very minimal. The

following chart shows the percentage in which the Future Flexible Design had the highest NPV:

Fig. 4. Highest ENPV Count Percentage



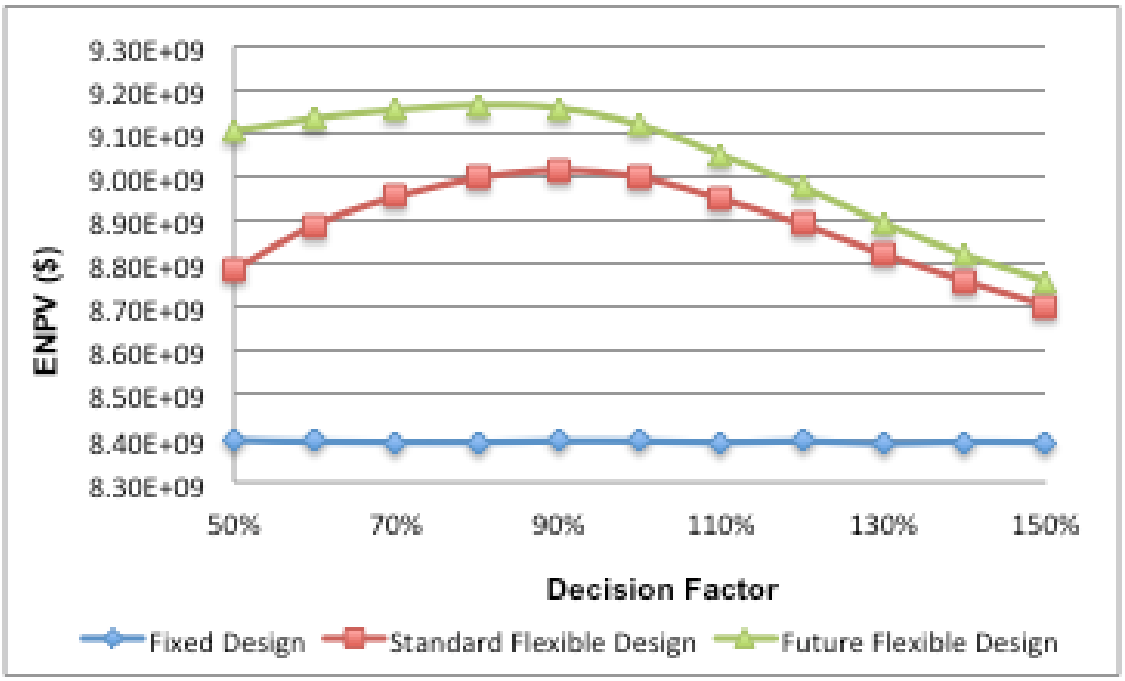
*note: 1 – Fixed Facility (not pictured), 2 – Standard Flexible Facility, 3 – Future Flexible Facility

The Future Flexible Design was favored in 99.51% of the total number of trials, thus re-enforcing the decision to select this design. Such NPVs arise when the trial has extremely high CAGR values in years 1-10 and years 11-20. In those situations, the costs of using disposable bioreactors outweigh those of operating large-scale stainless steel reactors. Based on the overall results of the simulation, there are obvious benefits to employing a flexible design.

Sensitivity Analysis

Simulations were conducted to analyze how changing the decision factor would affect the ENPVs for each of the designs. 10,000-trial Monte-Carlo simulations were conducted for design factors ranging from 50% to 150% in increments of 10%. The following chart shows how the mean ENPVs varied when running the simulations with different decision factors:

Fig. 5. Mean ENPV Versus Decision Factor

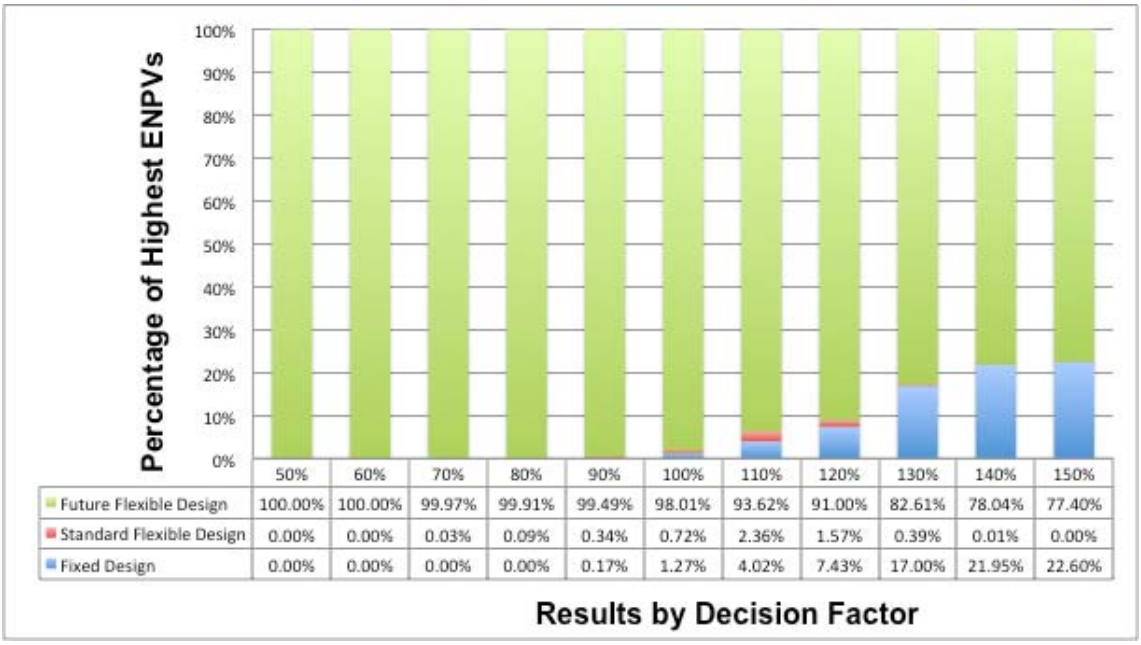


*note: the Fixed Design ENPV has minimal changes since there are no expansion capabilities; it is included only for reference

Even when demand exceeded capacity, the flexible design had higher mean ENPVs. Moreover, the Future Flexible Design had the highest mean ENPV for the range analyzed. The highest mean ENPV for the Standard Flexible Design was achieved at 90%, while the highest mean ENPV for the Future Flexible Design was achieved at 80% (though the values between 70% and 90% were very similar). This demonstrates how the 80% - 90% range for the decision factor is a “sweet spot” for maximizing revenue with the applied cost model. Past 90%, the mean ENPV decreases because product demand exceeds supply the company will not recover lost revenues even with facility expansion.

Another factor to consider is which designs had the highest ENPV in the simulation trials. The following chart shows the percentages in which each design had the highest ENPV for the range of decision factor:

Fig. 6. Highest ENPV Count Percentage Versus Decision Factors



	50%	60%	70%	80%	90%	100%	110%	120%	130%	140%	150%
Future Flexible Design	100.00%	100.00%	99.97%	99.91%	99.49%	98.01%	93.62%	91.00%	82.61%	78.04%	77.40%
Standard Flexible Design	0.00%	0.00%	0.03%	0.09%	0.34%	0.72%	2.36%	1.57%	0.39%	0.01%	0.00%
Fixed Design	0.00%	0.00%	0.00%	0.00%	0.17%	1.27%	4.02%	7.43%	17.00%	21.95%	22.60%

The Future Flexible Design had the highest ENPV in a large majority of the simulations. However, as the decision factor increased past 100%, the Fixed Design had the highest ENPV in a number of trials. The main reason for this occurrence is that the Fixed Design had the capacity to meet demand. With decision factors equal or greater than 100% for the flexible designs, product demand will exceed capacity in certain years. As a result, there will be a certain amount of lost revenue.

Discussion

Based on the results of this assessment, the flexible designs generally outperformed the Fixed Design, and the Future Flexible Design should be selected for the production of Nishumab. This is based on the ENPV performance for the following criteria: Min, Mean, Standard Deviation, P_5, and P_{95} values. The flexible designs, especially the Future Flexible Design, are most applicable when product demand growth rates are modest. However, in the rare cases of extreme demand growth, the Fixed and Standard Flexible Designs could prove to be more valuable. Due to the dependence on disposable bioreactors, the operational costs associated with the Future Flexible Design increase significantly with extremely high demand CAGRs. Moreover, expansion capabilities could be limited since you would be dependent on a supplier for the disposable

bioreactors (i.e. three-layer plastic bags). This is a consideration that a biotech company must tackle when deciding to employ a Future Flexible Design.

The simulation conducted was the most appropriate analysis method given the following:

- Market demand growth rates fluctuated on a per-year basis (i.e. not static). Therefore, a lattice model would not be appropriate.
- A range of NPVs needed to be analyzed for each design. A decision tree would have been more difficult to implement in this case, because the range would have exploded into hundreds of branches. It would have been a prime example of the dimensionality curse when employing a decision tree.

While the analysis focused operating and capital costs for manufacturing, it would be worthwhile to conduct a decision analysis taking drug development costs and results into account. For instance, many biotech companies may elect to outsource manufacturing rather than build a facility; this is favored option when supplying product for clinical trials, where there is a significant chance that the drug will not be available commercially. A decision tree could be completed to determine whether it is more cost-effective to build a facility or to outsource to a contract manufacturer. However, in order to complete the analysis, one must have a deep understanding of drug development and physiology to determine the success rates of therapies. In addition, R&D expenses could be more accurately predicted with such knowledge.

For me, this application portfolio helped me to learn more about the key manufacturing strategies in the industry. In addition, I learned how to perform an NPV simulation analysis on design models that I created based on industry research and my knowledge of the production process. I hope to continue doing NPV analyses in my career, and the skills I learned in this course will certainly aid me. My experience, prior to this, was mainly in process and control system engineering. I used to support equipment used in the production of mAbs, and I was keen to gain exposure to manufacturing cost analysis. It is one the hottest segments in biotech today, and that the trend could stay for at least the next 10 years (10). Therefore, manufacturers need to prepare for an increasing number of products. One way to do that is to construct and validate a facility to handle multiple products, assuming that the company was selling more than one monoclonal

antibody therapeutic. On the other hand, several pharmaceutical manufacturers have had to deal with overcapacity issues in recent years due to increased regulations on drug usage that resulted in decreasing product demand. They employed a fixed design and assumed that product demand would rapidly grow and are now left with unused manufacturing equipment. Using a flexible design can help in preventing overcapacity issues in the future.

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APPENDIX A – EXCEL SCREENSHOTS

Fixed Facility NPV

Fixed Facility Simulation

Year	0	1	2	3	.....	20
No. of Trains		6	6	6	.....	6
No. of Employees		300	300	300	.....	300
Capacity		6,750,000	6,750,000	6,750,000	.....	6,750,000
Demand		1,000,000	1,065,000	1,134,225	.....	2,148,563
Production		1,000,000	1,065,000	1,134,225	.....	2,148,563
Revenue		$2,000,000,000.00	$2,130,000,000.00	$2,268,450,000.00	.....	$4,297,126,940.33
Costs:						
Depreciation		$ 25,000,000.00	$ 25,000,000.00	$ 25,000,000.00	.....	$ 25,000,000.00
Raw Materials		$ 10,000,000.00	$ 10,650,000.00	$ 11,342,250.00	.....	$ 21,485,634.70
Labor		$ 45,000,000.00	$ 45,000,000.00	$ 45,000,000.00	.....	$ 45,000,000.00
Maintenance & Projects		$ 30,000,000.00	$ 30,000,000.00	$ 30,000,000.00	.....	$ 30,000,000.00
Fill/Finish & Distribution		$ 80,000,000.00	$ 85,200,000.00	$ 90,738,000.00	.....	$ 171,885,077.61
Inventory		$ 100,000,000.00	$ 106,500,000.00	$ 113,422,500.00	.....	$ 214,856,347.02
Total Costs (COGS) w/ Inflation		$ 290,000,000.00	$ 310,670,500.00	$ 333,194,367.48	.....	$ 872,341,573.55
Profit		$1,710,000,000.00	$1,819,329,500.00	$1,935,255,632.53	.....	$3,424,785,366.78
SG&A		$ 600,000,000.00	$ 639,000,000.00	$ 680,535,000.00	.....	$1,289,138,082.10
R&D Re-investment		$ 400,000,000.00	$ 426,000,000.00	$ 453,690,000.00	.....	$ 859,425,388.07
Net Income (EBIT)		$ 710,000,000.00	$ 754,329,500.00	$ 801,030,632.53	.....	$1,276,221,896.62
Capitol Investment	$ 500,000,000.00	$ -	$ -	$ -	.....	$ -
Additional Investments		$ -	$ -	$ -	.....	$ -
Salvage Value		$ -	$ -	$ -	.....	$ -
Total Year Value		$ 710,000,000.00	$ 754,329,500.00	$ 801,030,632.53	.....	$1,276,221,896.62
Discount Factor		10%	10%	10%	.....	10%
Present Value		$ 645,454,545.45	$ 623,412,809.92	$ 601,826,170.19	.....	$ 189,702,252.88
NPV	$7,963,664,258.17					

- Values for years 4 – 19 are hidden for presentation purposes
- Since the design is fixed, there were no expansions over the time horizon (20 years

Standard Flexible Facility NPV

Standard Flexible Facility Simulation

Year	0	1	2	3	.....	13	14	15	.....	20
No. of Trains		2	2	2	.....	2	3	4	.....	4
No. of Employees		120	120	120	.....	120	165	210	.....	210
Capacity		2,250,000	2,250,000	2,250,000	.....	2,250,000	3,375,000	4,500,000	.....	4,500,000
Demand		1,000,000	1,065,000	1,134,225	.....	1,870,454	1,907,863	1,946,020	.....	2,148,563
Production		1,000,000	1,065,000	1,134,225	.....	1,870,454	1,907,863	1,946,020	.....	2,148,563
Revenue		$2,000,000,000.00	$2,130,000,000.00	$2,268,450,000.00	.....	$3,740,907,596.70	$3,815,725,748.64	$3,892,040,263.61	.....	$4,297,126,940.33
Costs:										
Depreciation		$ 15,000,000.00	$ 15,000,000.00	$ 15,000,000.00	.....	$ 15,000,000.00	$ 20,507,001.43	$ 26,179,212.89	.....	$ 26,179,212.89
Raw Materials		$ 10,000,000.00	$ 10,650,000.00	$ 11,342,250.00	.....	$ 18,704,537.98	$ 19,078,628.74	$ 19,460,201.32	.....	$ 21,485,634.70
Labor		$ 18,000,000.00	$ 18,000,000.00	$ 18,000,000.00	.....	$ 18,000,000.00	$ 24,750,000.00	$ 31,500,000.00	.....	$ 31,500,000.00
Maintenance & Projects		$ 15,000,000.00	$ 15,000,000.00	$ 15,000,000.00	.....	$ 15,000,000.00	$ 22,500,000.00	$ 30,000,000.00	.....	$ 30,000,000.00
Fill/Finish & Distribution		$ 80,000,000.00	$ 85,200,000.00	$ 90,738,000.00	.....	$ 149,636,303.87	$ 152,629,029.95	$ 155,681,610.54	.....	$ 171,885,077.61
Inventory		$ 100,000,000.00	$ 106,500,000.00	$ 113,422,500.00	.....	$ 187,045,379.84	$ 190,786,287.43	$ 194,602,013.18	.....	$ 214,856,347.02
Total Costs (COGS) w/ Inflation		$ 238,000,000.00	$ 257,410,500.00	$ 278,636,567.48	.....	$ 568,745,883.87	$ 622,229,800.19	$ 678,474,191.56	.....	$ 849,848,454.73
Profit		$1,762,000,000.00	$1,872,589,500.00	$1,989,813,432.53	.....	$3,172,161,712.83	$3,193,495,948.45	$3,213,566,072.05	.....	$3,447,278,485.61
SG&A		$ 600,000,000.00	$ 639,000,000.00	$ 680,535,000.00	.....	$1,122,272,279.01	$1,144,717,724.59	$1,167,612,079.08	.....	$1,289,138,082.10
R&D Re-investment		$ 400,000,000.00	$ 426,000,000.00	$ 453,690,000.00	.....	$ 748,181,519.34	$ 763,145,149.73	$ 778,408,052.72	.....	$ 859,425,388.07
Net Income (EBIT)		$ 762,000,000.00	$ 807,589,500.00	$ 855,588,432.53	.....	$1,301,707,914.48	$1,285,633,074.13	$1,267,545,940.24	.....	$1,298,715,015.44
Capitol Investment	$ 300,000,000.00	$ -	$ -	$ -	.....	$ -	$ -	$ -	.....	$ -
Additional Investments		$ -	$ -	$ -	.....	$ -	$ 110,140,028.51	$ 113,444,229.36	.....	$ -
Salvage Value		$ -	$ -	$ -	.....	$ -	$ -	$ -	.....	$ 151,001,979.09
Total Year Value		$ 762,000,000.00	$ 807,589,500.00	$ 855,588,432.53	.....	$1,301,707,914.48	$1,175,493,045.62	$1,154,101,710.88	.....	$1,449,716,994.53
Discount Factor		10%	10%	10%	.....	10%	10%	10%	.....	10%
Present Value		$ 692,727,272.73	$ 667,429,338.84	$ 642,816,252.84	.....	$ 377,058,415.65	$ 309,544,058.13	$ 276,282,773.75	.....	$ 215,491,193.67
NPV	$8,581,356,739.23									

- Values for years 4 – 12 and 16 – 19 are hidden for presentation purposes
- The decision formula applied for “No. of Trains” is as follows (example for year 15):

  =MIN(IF(O9>('Control Center'!$J$32*O8),P5+'Control Center'!$J$27,P5),'Control Center'!$J$26)
  - Values can be found in the Cost Model(e.g. Control Center J26 = 6)
  - This formula accounts for the year taken to implement the expansion
  - Employee and Additional Investments were updated based on increases in the number of trains

Future Flexible Facility NPV

Future Flexible Facility Simulation

Year		0	1	2	3	.....	13	14	15	.....	20
No. of Trains			15	15	15	.....	15	20	25	.....	25
No. of Employees			120	120	120	.....	120	126	132	.....	132
Capacity			2,250,000	2,250,000	2,250,000	.....	2,250,000	3,000,000	3,750,000	.....	3,750,000
Demand			1,000,000	1,065,000	1,134,225	.....	1,870,454	1,907,863	1,946,020	.....	2,148,563
Production			1,000,000	1,065,000	1,134,225	.....	1,870,454	1,907,863	1,946,020	.....	2,148,563
Revenue			$2,000,000,000.00	$2,130,000,000.00	$2,268,450,000.00	.....	$3,740,907,596.70	$3,815,725,748.64	$3,892,040,263.61	.....	$4,297,126,940.33
Costs:						.....				.....	
Depreciation			$ 10,000,000.00	$ 10,000,000.00	$ 10,000,000.00	.....	$ 10,000,000.00	$ 11,835,667.14	$ 13,726,404.30	.....	$ 13,726,404.30
Raw Materials			$ 20,000,000.00	$ 21,300,000.00	$ 22,684,500.00	.....	$ 37,409,075.97	$ 38,157,257.49	$ 38,920,402.64	.....	$ 42,971,269.40
Labor			$ 18,000,000.00	$ 18,000,000.00	$ 18,000,000.00	.....	$ 18,000,000.00	$ 18,900,000.00	$ 19,800,000.00	.....	$ 19,800,000.00
Maintenance & Projects			$ 4,500,000.00	$ 4,500,000.00	$ 4,500,000.00	.....	$ 4,500,000.00	$ 6,000,000.00	$ 7,500,000.00	.....	$ 7,500,000.00
Fill/Finish & Distribution			$ 80,000,000.00	$ 85,200,000.00	$ 90,738,000.00	.....	$ 149,636,303.87	$ 152,629,029.95	$ 155,681,610.54	.....	$ 171,885,077.61
Inventory			$ 100,000,000.00	$ 106,500,000.00	$ 113,422,500.00	.....	$ 187,045,379.84	$ 190,786,287.43	$ 194,602,013.18	.....	$ 214,856,347.02
Total Costs (COGS) w/ Inflation			$ 232,500,000.00	$ 252,565,000.00	$ 274,530,110.50	.....	$ 575,443,593.22	$ 608,754,346.92	$ 643,726,114.93	.....	$ 815,100,929.62
Profit			$1,767,500,000.00	$1,877,435,000.00	$1,993,919,889.50	.....	$3,165,464,003.48	$3,206,971,401.71	$3,248,314,148.68	.....	$3,482,026,010.71
SG&A			$ 600,000,000.00	$ 639,000,000.00	$ 680,535,000.00	.....	$1,122,272,279.01	$1,144,717,724.59	$1,167,612,079.08	.....	$1,289,138,082.10
R&D Re-investment			$ 400,000,000.00	$ 426,000,000.00	$ 453,690,000.00	.....	$ 748,181,519.34	$ 763,145,149.73	$ 778,408,052.72	.....	$ 859,425,388.07
Net Income (EBIT)			$ 767,500,000.00	$ 812,435,000.00	$ 859,694,889.50	.....	$1,295,010,205.13	$1,299,108,527.40	$1,302,294,016.87	.....	$1,333,462,540.55
Capitol Investment	$ 200,000,000.00		$ -	$ -	$ -	.....	$ -	$ -	$ -	.....	$ -
Additional Investments			$ -	$ -	$ -	.....	$ -	$ 36,713,342.84	$ 37,814,743.12	.....	$ -
Salvage Value			$ -	$ -	$ -	.....	$ -	$ -	$ -	.....	$ 50,333,993.03
Total Year Value			$ 767,500,000.00	$ 812,435,000.00	$ 859,694,889.50	.....	$1,295,010,205.13	$1,262,395,184.56	$1,264,479,273.75	.....	$1,383,796,533.58
Discount Factor			10%	10%	10%	.....	10%	10%	10%	.....	10%
Present Value			$ 697,727,272.73	$ 671,433,884.30	$ 645,901,494.74	.....	$ 375,118,327.82	$ 332,428,107.38	$ 302,706,284.73	.....	$ 205,692,537.20
NPV	$8,754,940,378.24										

- Values for years 4 – 12 and 16 – 19 are hidden for presentation purposes
- The decision formula applied for “No.of Trains” is as follows (example for year 15):

  =MIN(IF(O9>('Control Center'!$K$32*O8),P5+'Control Center'!$K$27,P5),'Control Center'!$K$26)
  - Values can be found in the Cost Model (e.g. Control Center K26 = 45)
  - This formula accounts for the one year taken to implement the expansion
  - Employee and Additional Investments were updated based on increases in the number of trains