Drug Substance and Drug Product Manufacturing Strategy Assessment for siRNAs

by

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Submitted to the
MIT Sloan School of Management and
MIT Department of Civil and Environmental Engineering
in partial fulfillment of the requirements for the degrees of
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Abstract

Amgen currently has its first siRNA program, Asset #1 in phase 2 clinical trials. Until recently, Amgen has been outsourcing the Drug Substance (DS) and Drug Product (DP) manufacturing to external manufacturers, but with a growing siRNA portfolio even beyond Asset #1, the building of a new facility is of great interest and value.

As there are hundreds of potential manufacturing scenarios, this thesis will first shortlist those into three most feasible ones to be analyzed with a supply chain model and eventually a business model. The supply chain model will include resilience and weak link analysis, which will result in a risk-to-cost input for the overall business model, currently built only for Asset #1 due to limited information on other assets in earlier development phases. The business model, equipped with mixed integer program, calculates the 20-year Present Value of Expense (PV of Expense) to identify the optimal capacity progression and scenario, even beyond the three predefined ones, with the least expense.

It was eventually found that the best scenario is indeed beyond the three predefined ones, suggesting internalization very soon after Asset #1's commercial launch. However, it is decided on the delay to see what product demand would be, so that Amgen would only invest if the program showed a need/showed a profitable outcome. It is recommended that Amgen keep updating the model and continue monitoring the market to understand supply and demand dynamics on siRNA, as well as innovating on Amgen's siRNA process.

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Chapter 1

Introduction

Small Interfering RNA (siRNA) is a new class of therapeutics with the potential to treat diseases by inhibiting the expression of a gene. This class of molecules was first reported in 1999 and later recognized with the 2006 Nobel Prize in medicine. It became a viable class of therapeutics since the approval of the first siRNA therapeutic in 2018, Onpattro® by Alnylam. A second siRNA therapeutic, Givlaari® from Alnylam, was approved in 2019.

1.1 Background

The central dogma of protein synthesis follows three sequential steps, beginning with DNA, transcribed into mRNA, which is then translated into protein. In some cases, a particular protein is not desired. The production of that certain protein can be avoided with "gene silencing", a regulation of gene expression in a cell to prevent the expression of a certain gene. Gene silencing has massive potential for research, as well as for gene therapy applications. In order to silence a gene, one may target the DNA-mRNA step, or the mRNA-protein step of the protein synthesis process. For the former, silencing of the transcription involves influencing the DNA or the organism via genetic engineering. This is relatively unfavorable in many applications, as changing the genome may produce

undesired effects and have ethical complications. Therefore, many choose to use RNA interference through siRNA as a means of gene silencing.

Amgen began its first siRNA program, Asset #1, in 2017, about ten years after siRNA was recognized with a Nobel Prize in medicine. As this is a new modality, there are a limited number of manufacturers with the capability to produce these complex synthetic biopolymers with the appropriate capacity, quality, and regulatory compliance. As Amgen's first siRNA program, an appropriate large-scale manufacturing facility does not exist within the Amgen-owned network.

1.2 Problem Statement

Until recently, Amgen has been outsourcing the drug substance and drug product manufacturing to external manufacturers, but with a growing siRNA portfolio and the indication that siRNA effectiveness is promising, the building of a new facility is of great interest and value. This thesis helps Amgen shape its siRNA manufacturing strategy – whether Amgen should build a new facility to internalize its production or continue to outsource, and if the answer is the former, when should they start internalizing.

In general, this thesis aims to answer the following questions:

1. How does siRNA drug substance and drug product manufacturing fit with Amgen's current manufacturing network and strategy?

2. How should Amgen design the drug substance's manufacturing process, equipment, and shifts if Amgen internalizes siRNA manufacturing? What is the cycle time, run time, and maximum capacity annually? How should Amgen expand the facility, or "suite", based on the increasing demand projection (i.e., increase shift, add new equipment, or add new suite)?

3. Should Amgen build a new facility or use an existing one to manufacture siRNA drug substance and drug product in-house? If yes, when should Amgen start internalizing?

1.3 Project Approach

The project is completed in the following overlapping stages:

1. Team engagement
2. Business model creation
3. Manufacturing process and facility design creation
4. Supply chain model creation
5. Data collection
6. Model trials and simulation
7. Proposal/recommendation

Team engagement

Identifying relevant teams to work with on each sub-piece of the main model deliverable is the first key step in this project. Creating connections, as well as regular touchpoints and discussions are vital for long term success. Understanding stakeholders, the manufacturing process, availability of Amgen's capabilities and capacity directly impacted by the project is important to ensuring buy-in and support for the project.

Business model creation

While working with relevant teams to gather data, a skeleton/framework and assumptions of the final business model are created using dummy data. The objective of this step is to get upfront alignment on the model set-up and assumptions, which will not only increase the efficiency of later steps of the project (i.e., plugging in the sub-pieces' data into the

general model that is already working and aligned), but also ensure buy-in from key stakeholders responsible for the continuity of this project. These activities are key to ensuring the utility of the project's conclusions. The model is investigated or modified as necessary to account for dependencies resurfacing in the later stage. This model, fed with the real data input, is the final deliverable of this project.

Manufacturing process and facility design creation

As an input for the business model, a manufacturing process and facility design were created. This includes the process planning, e.g., the volume ratio of antisense and sense strand to be annealed, the sequence of production (i.e., antisense-antisense-sense vs. antisense-sense-antisense, etc.), and the manufacturing equipment needed. Additionally, this step also helps to identify equipment lists, maximum capacity per suite, and labor planning, all of which are critical components for the business model.

Supply chain model creation

For every scenario appearing in the business model, a subsequent supply chain model is made. Stress-testing and resilience check are performed based on the supply chain model, and the results are translated from risk into cost, to serve as an input to the business model. Besides quantitative results, the supply chain model is also used to help making qualitative decisions. Since RNAi molecules are a relatively new class of therapeutics, the raw material supply chain is not as established as for other molecules and therapeutics, so a better understanding in this aspect can drive a more informed final decision.

Data collection

Data are gathered from relevant teams to be the inputs for the business model. To ensure timeliness, relevancy, and fit with the model, a close working relationship is necessary, i.e., joining regular team meetings, giving input, etc. Data collection is a key activity, as

the final run of the model is highly dependent on the collected data. It is imperative that data sources and assumptions are understood and clearly documented so that the output of the business model can be correctly interpreted.

Model trials and simulation

Once data is fed into the model, scenario trials and simulation are carried out. Comparison exercises, both quantitative and qualitative, of the model's results for different scenarios are performed to prescribe recommendations on the desirable business process.

Proposal/recommendation

Based on the model output, a recommendation for make (Amgen internal manufacturing) or buy (manufacturing by an external partner) is made along with a suggested timeline for investment.

1.4 Thesis Structure

This thesis is organized as follows:

Chapter 2 – Background on Current State presents an overview of how siRNA works, the current state of siRNA production in detail, as well as the manufacturing steps of a typical siRNA synthetic process.

Chapter 3 – Literature Review of academic articles that discuss siRNA on its development and delivery progress in the past until now, and a view in the future, looking at the potential of RNA vaccines. It also presents research and the potential of green chemistry in siRNA manufacturing to make it more environmentally friendly.

Chapter 4 – Scenario Selection of siRNA Manufacturing Strategy sets the stage for the subsequent chapters by introducing shortlisted scenarios for further analysis. This chapter introduces the complexity of hundreds of potential siRNA

manufacturing strategies and delves into the most feasible ones for supply chain and business case analysis.

Chapter 5 – Supply Chain Model presents the methodology to analyze supply chain resilience and its weak links, making it possible to compare the resilience of the shortlisted scenarios. This analysis results in an input for the business model.

Chapter 6 – Business Model dives deep into the business model creation, optimization model, and sensitivity analysis. Having identified multiple inputs for the business model, the Present Value of Expense (PV of Expense) are compared among the shortlisted scenarios, making it possible to identify the scenario with the least PV of Expense. Additionally, mixed integer programs are used to pursue multiple optimization efforts to further optimize the model beyond the shortlisted scenarios.

Chapter 7 – Conclusions and Recommendations concludes the project with a discussion on preliminary recommendations, as well as suggested next steps to implement the recommendations and to update the model for future works – i.e., for future siRNA assets and other assets than siRNA.

Chapter 2

Background on Current State

This chapter gives background on siRNA way of working, as well as the siRNA creation process and manufacturing.

2.1. How siRNA Works

Small interfering RNA, or siRNA, is a class of double-stranded RNA that functions to regulate gene expression through the process of RNA interference (RNAi). RNAi is a natural process that occurs in cells to stop a gene from producing a particular protein. As a double-stranded RNA, siRNA consists of sense-strand and antisense-strand. Sense strand, or coding strand, carries the translatable code in the $5'$ to $3'$ direction, and which is complementary to the antisense strand, or template strand, which does not carry the translatable code in the $5'$ to $3'$ direction. Proteins are made in carefully prescribed steps: first the DNA sequence of a gene is transcribed into a molecule called a messenger RNA (mRNA); next the mRNA sequence – carrying over the gene's sequence – is translated into the corresponding amino acid sequence or protein. siRNA stops the production, and therefore activity, of a protein by interfering with the mRNA and preventing its translation into protein. siRNAs work by degrading mRNA in a highly specific manner.

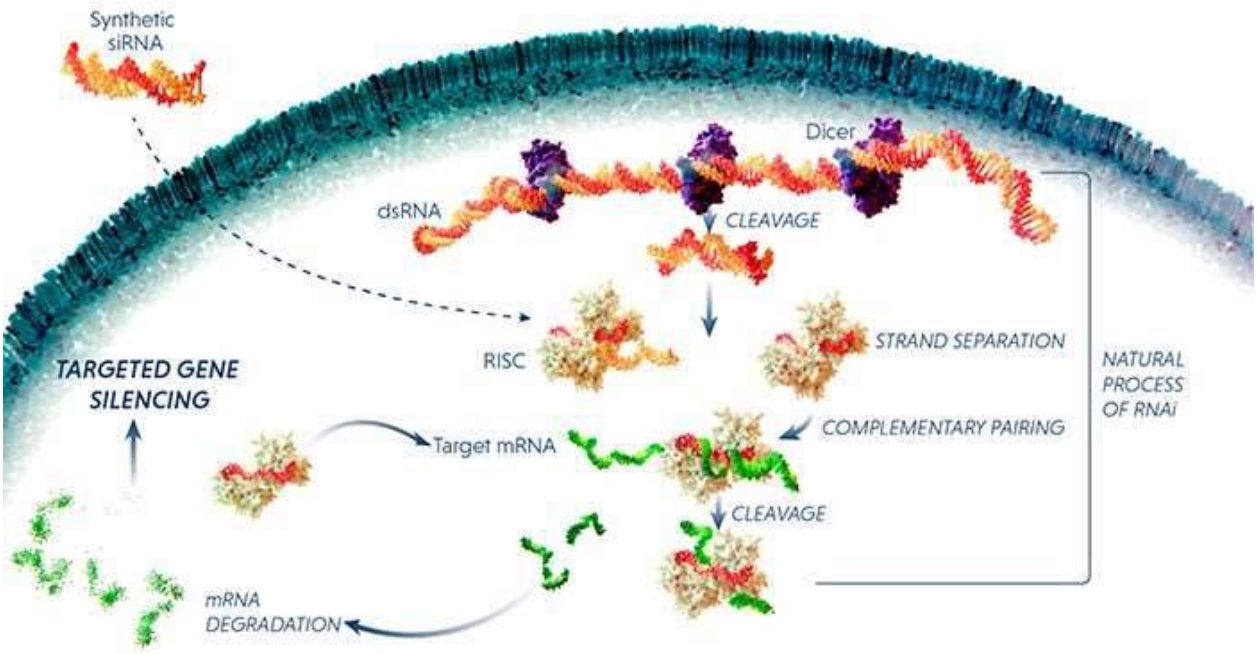

Figure 2-1. How siRNA Works (Alnylam, accessed March 2021)

Once an mRNA sequence of interest is known, the siRNA molecule can be designed with a complementary sequence that is able to target the mRNA and cause its destruction. A double-strand, 21-25 nucleotides long, siRNA complementary to the target mRNA is produced in the laboratory and inserted to the cell cytoplasm. Once it is inside the cell, the antisense strand binds to proteins such as Argonaute-2 (Ago2) and Transactivating Response RNA Binding-Protein (TRBP) to form the RNA Induced Silencing Complex, or RISC, while the sense strand is discarded. When the mRNA leaves the nucleus to be translated into protein, the RISC binds the complementary sequence and associates with the mRNA via complementary base pairing. RISC then cleaves the mRNA strand in the middle of the targeted sequence. The cleaved mRNA is then rapidly degraded in the cell, before it even has the chance to make the protein. Without the mRNA, protein synthesis is effectively stopped. The siRNA therapeutic approach – stopping the production of an undesirable protein before it has even been made – has been described as "stopping the

flood by turning off the faucet as compared to today's medicines that simply mop up the floor". (Conlon, Nicole A. and Royzman, Irena, August 2018, at Patterson Belknap).

2.2. siRNA Manufacturing

To simplify siRNA production above, generally, siRNA drug manufacturing process can be broken down into four main steps:

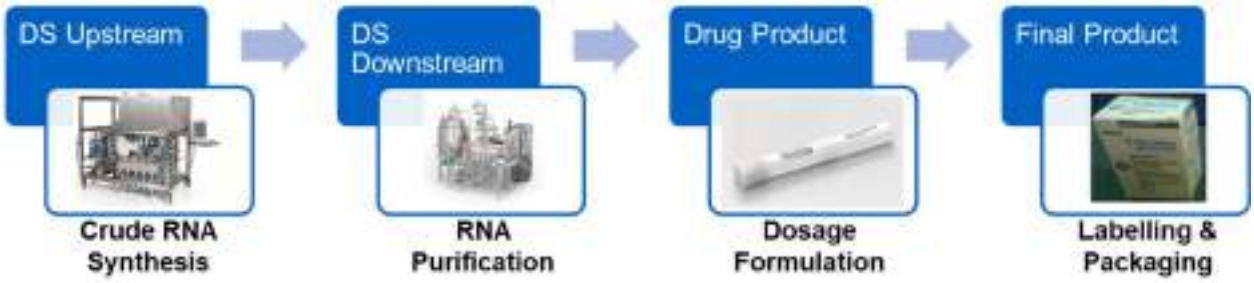

Figure 2-2. siRNA Manufacturing Process

1. **Drug substance (DS) – Upstream**

   The upstream manufacturing process is what produces the crude drug substance. This step consists of two stages. The first stage is solid phase synthesis, in which each RNA strand is manufactured on a solid support. Once a strand is made, it is moved to the second stage: cleavage and deprotection, removing the strand from the support and the protecting groups from the chain.

2. **Drug substance (DS) – Downstream**

   The downstream process purifies the crude drug substance to an acceptable final purity for use and delivers a form that can be used to manufacture the drug product. Continuing from upstream, the third stage is UF/DF (Ultrafiltration/Diafiltration) to remove chemical reagents and byproducts from the crude single strand. Then, the

fourth stage is chromatography to purify each RNA strand. The fifth stage is another UF/DF to remove salts from the purification and to deliver each single RNA strand as a solution in water. Both strands of the double-stranded siRNA molecule are synthesized and purified separately, and they are mixed in a 1-to-1 ratio to make the final siRNA molecule in the annealing step. The last stage is lyophilization where the siRNA solution is freeze-dried to produce the drug substance as a white powder.

3. **Drug product (DP)**

   Once in this step, the drug substance previously manufactured is dissolved in the final formulation buffer, sterilized, and then filled into the appropriate dosage form for use. The drug is filled in vials, pre-filled syringes, or autoinjectors.

4. **Final drug product (FDP)**

   The final manufacturing step labels and packages the final product in accordance with regulatory commitments and complete with dosing and use instructions for doctors and patients. This step only exists in clinical trial phase 3 and commercial production.

Chapter 3

Literature Review

This chapter presents some research papers and articles about siRNA, specifically its potential on future gene therapy and vaccines for COVID-19, as well as its future manufacturing progression on green chemistry to be more environmentally friendly.

3.1. mRNA Vaccines

Development of vaccines against infectious pathogens is the most efficient means to contain and prevent epidemics. However, conventional vaccine approaches have largely failed to produce effective vaccines against challenging viruses in a quick manner, such as HIV-1, herpes simplex virus, Ebola, Zika, and recently, Coronavirus. Therefore, the development of more potent and versatile vaccine platforms is crucial. Preclinical studies have created hope that mRNA vaccines will fulfill many aspects of an ideal clinical vaccine: they have shown a favorable safety profile in animals, are versatile and rapid to design for emerging infectious diseases and are amendable to scalable good manufacturing practice (GMP) production (Pardi N., *et al.*, 2018).

Unlike protein immunization, several formats of mRNA vaccines induce strong CD8+ T cell responses, likely owing to the efficient presentation of endogenously produced

antigens of MHC class I molecules, in addition to potent CD4+ T cell responses (Schnee M., *et al.*, 2016). Additionally, unlike DNA immunization, mRNA vaccines have shown the ability to generate potent neutralizing antibody responses in animals with only one or two low-dose immunizations (Pardi N., *et al.*, 2017). There are three well-known vaccines methodology of mRNA. First is self-amplifying mRNA vaccines (SAM), where the genes encoding the RNA replication machinery are intact but the genes encoding the structural proteins are replaced with the antigen of interest. Some studies include influenza virus in mice (Fleeton M. N., *et al.,* 2001). The second one is dendritic cell (DC) mRNA vaccines, which is an *ex vivo* methodology, heavily researched for HIV (Van Gluck E., *et al.*, 2012). The third one is direct injection of non-replicating mRNA vaccines. Directly injectable, non-replicating mRNA vaccines are an appealing vaccine format owing to their simple and economical administration. Some studies of this include vaccines against influenza in mice (Martinon F., *et al.,* 1993) and rabies in pigs (Schnee M., *et al.*, 2016).

Fighting the current COVID-19 pandemic, Pfizer/BioNTech and Moderna vaccines are both mRNA-based and have been successfully implemented.

3.2. Green Chemistry for siRNA Manufacture

Along the years, there are key accomplishments that reduce or eliminate the use or generation of toxic materials, solvents, or reagents. Additionally, there have been methodologies that allow reuse of valuable materials such as amidites, solid-support, and protecting groups, thus improving the atom economy and cost-efficiency of oligonucleotide manufacture. According to Sanghvi Y. S*, et al.* (2001), the industry has made multiple modifications to large-scale oligonucleotide manufacturing processes to accommodate some of the twelve principles of green chemistry:

1. Prevention
2. Atom economy
3. Less hazardous chemical syntheses
4. Designing safer chemicals
5. Safer solvents and auxiliaries
6. Design for energy efficiency
7. Use of renewable feedstocks
8. Reduce derivatives
9. Catalysis
10. Design for degradation
11. Real-time analysis for pollution prevention
12. Safer chemistry for accident prevention

Replacement of fish-derived nucleosides with synthetic nucleosides

The first generation of antisense drugs required a key building block obtained via enzymolysis of DNA salt, which source has been isolated exclusively from fish milt, mainly from salmon caught for human consumption. The seventh principle of green chemistry states that raw material feedstocks should be renewable, not depleting whenever technically and economically practicable. Therefore, it is replaced with environmentally benign silyl reagents from a plant source, without compromising reaction yields. Thus, large-scale supplies are now fully independent of marine DNA sources.

Elimination of halogenated solvent and waste from manufacturing processes

Antisense oligonucleotides are made on solid supports, which crucial step requires removal of a protecting group with haloacetic (chloroacetic, specifically) acid, classically carried out in dichloromethane. Volatility, toxicity, and carcinogenicity issues have increasingly limited the use of dichloromethane in the chemical industry. In the context of the fourth principle of green chemistry, it is desired to find a replacement for dichloromethane. An extensive search identified toluene as a green substitute for dichloromethane, the former of which is also widely accepted due to its lower vapor pressure and well-established environmental fate.

Development of reusable solid-support for oligonucleotide synthesis

Solid-support selection has a significant impact not only on synthesis efficiency and product cost but also on the environment. Previously used solid-support was typically not biodegradable, could only be used once before disposal, contributed up to 40% of raw material costs, and was a single-source raw material. In view of these, there is a new methodology based on the use of a Q-linker^{TM} (hydroquinone diacetic acid) spacer arm between the 3'-end of the first nucleoside and a hydroxyl- functionalized support (Figure 3-1). In summary, the method allows used support to be quickly rederivated with protected nucleoside and reused, without opening and recharging the synthesis column. The solid support can be used six times in this technique, and thus the environmental impacts are sharply reduced.

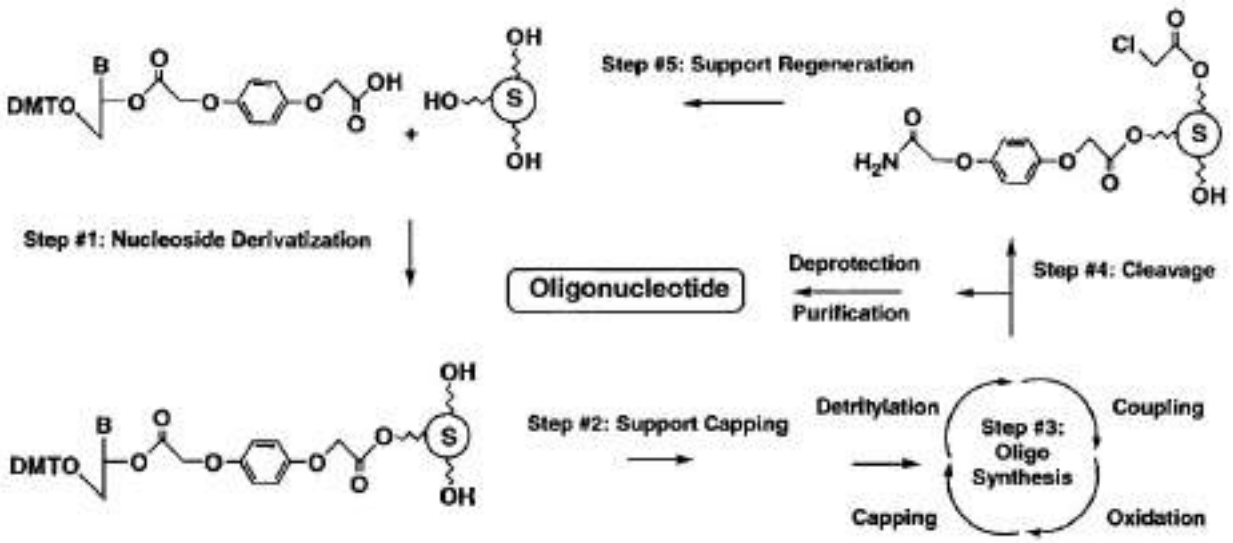

Figure 3-1. Reusable Solid-support Chemistry (Sanghvi Y. S, *et al.*, 2001)

Procedure for safer cleavage of protecting groups

The importance of safety in the chemical industry cannot be overstated. In the oligonucleotide manufacturing process, all steps but one is carried out at room temperature. In light of the twelfth principle of green chemistry, this step is carried out

under pressure at elevated temperatures. Cleavage of oligonucleotide from solid-support and heterocyclic base deprotection is accomplished by treatment with concentrated ammonium hydroxide at 55^{o}C in a sealed pressure vessel for 12 hours. Deprotection at ambient temperature and pressure would clearly reduce the risk of operator injury. Therefore, a systematic study of deprotection rate was carried out using phosphorothioate oligonucleotide drugs. The results indicated that all protecting groups are completely removed in 120 hours at 20^{o}C, including the difficult guanine isobutyryl protecting group. Ambient temperature and pressure deprotection are safer where extended reaction time is acceptable.

Use of water instead of organic solvent for chromatography

GMP antisense oligonucleotide intermediates are routinely purified using reverse phase (RP) chromatography. This method yields oligonucleotides of high purity and is readily scalable to multi-hundred kilogram per year levels. Because some antisense drugs have potential market annual requirements in the multi-ton range, an efficient chromatographic protocol, which operate entirely without organic solvent and its attendant hazards for use in very large-scale facilities, was developed.

Chapter 4

Manufacturing Strategy Scenario Selection

Due to the complexities of the potential scenarios of Amgen's siRNA manufacturing strategy, such as external vs. internal, using existing facility vs. building completely new ones, etc., key assumptions were made, and three scenarios were shortlisted three scenarios as the focus of the analysis in this thesis.

4.1. siRNA Development Timeline at Amgen

siRNA was first observed in flowers in 1999, then in 2006 it was recognized with the Nobel Prize for Physiology or Medicine by Fire and Mello. In 2017, Amgen selected its first siRNA program, Asset #1. Currently, Amgen has multiple siRNA program in development, with Asset #1 in clinical trial phase 2 and advancing towards the market.

Until recently, Amgen outsources the drug substance and drug product manufacturing of siRNA therapeutics to external manufacturers. However, with a growing siRNA portfolio and with the industry trend going towards siRNA, the building of a new facility is of great interest and value.

Figure 4-1. siRNA Development Timeline, General and at Amgen

4.2. Scenario Selection

Of the four main steps of siRNA manufacturing procedure, detailed out in Section 2.3., each can be either outsourced or internalized – for the last three steps specifically, Amgen can either use existing facilities or build a new one dedicated for siRNA. With additional complexities such as whether lyophilization is necessary, and whether, a hybrid-type of facility with single-use equipment is desired in the case that Amgen builds a new facility, there are hundreds of possible combinations or potential scenarios. Figure 4-2 below illustrates the complexities of only one factor – external vs. internal. For example, there are two potential ways to do DS upstream – CMO (Contract Manufacturing Organization) or new internal facility – each of which will also have two potential ways to do DS downstream – CMO or new internal facility. In this step, there have been four potential paths from DS upstream to DS downstream. Thereafter, for each of the four potential paths, there are three potential ways to do DP – CMO, new internal facility, or existing internal facility – making the possible paths of manufacturing until this step into 12, and when it reaches FDP, there are 24 possible paths. Remember that this is only for clinical,

there are also commercial, and even other assets beyond Asset #1. The complexity just multiplies and the number of potential paths to manufacture siRNA increases rapidly.

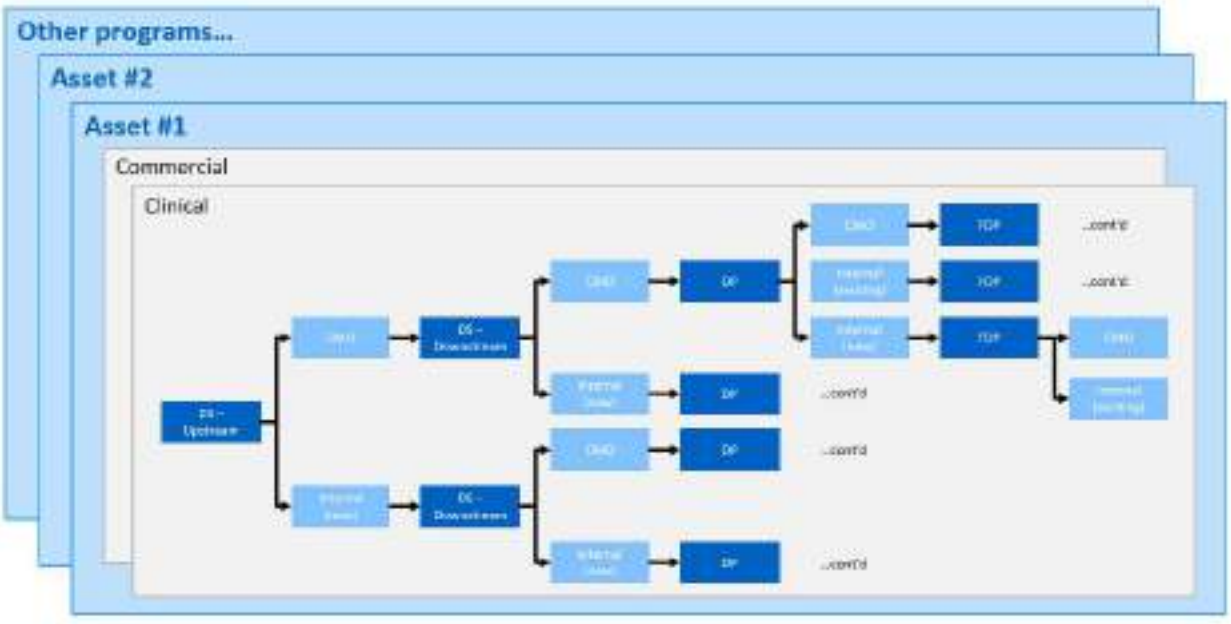

Figure 4-2. Illustration of the Complexity of Potential Manufacturing Strategies

Some of the next-level complexities in addition to the figure above are below, which increase the number of potential scenarios by an order of magnitude:

- External vs. internal
- Building a new facility vs. using an existing facility
- If building a new facility, a new building vs. a new suite in an existing building
- If building a new facility, hybrid type with single-use equipment vs. fixed equipment
- If building a new facility, Thousand Oaks vs. other locations
- Lyophilized drug substance vs. liquid drug substance

4.3. Three Shortlisted Scenarios

To have a more focused analysis, seven key assumptions are made.

1. **Make the analysis for Asset #1 only**

   For this analysis, Asset #1 is considered the only siRNA drug to be manufactured, since Asset #1 is the only siRNA drug at Amgen that already has demand projection, as well as robust raw material and process analysis.

2. **Use liquid drug substance, instead of lyophilized**

   There are three reasons why it is decided to assume liquid drug substance instead of a typical lyophilization manufacturing process. Lyophilization is usually chosen for product stability considerations, and these assumptions are based upon an asset having appropriate stability. First, if Amgen wants to internalize the drug product, Amgen's in-house drug product plant has only been receiving and processing liquid drug substance, thus lyophilization will require a new capability for the drug product facility. Second, lyophilization requires a lot of investment and adds around 5-7 days in the cycle time, reducing the capacity of the potential plant quite significantly. Third, based on the latest research and trial by the Drug Substance Team at Amgen, the liquid form of drug substance can be delivered by distillation instead of lyophilization, which requires much less investment and cycle time.

3. **If DS manufacturing is internalized, make a completely new facility**

   Even though the downstream part of the drug substance manufacturing process is an existing capability at Amgen, because it uses the same equipment and techniques that Amgen has for other processes, Amgen would prefer not to use an existing facility. Because existing facilities are designed for biologics manufacture, they do not have the proper safety controls like fire-rated construction and air handling and were not

designed to handle large quantities of organic solvents, which is largely required for siRNA manufacturing. Therefore, it is decided to assume that if Amgen internalizes the drug substance manufacturing, Amgen will create a completely new facility.

4. **DP manufacturing process can use existing facilities if internalized**

   Even though Amgen has also been outsourcing the drug product manufacturing process of siRNA to their external vendor, since it is assumed that Amgen is using liquid drug substance, and there is no difference in the drug product manufacturing process compared to what Amgen has been doing, this analysis assumes that, if internalized, Amgen can use the existing drug product manufacturing facility without any alteration.

5. **Final product assembly process is always in-house**

   Similar to the drug product manufacturing process, final product assembly for siRNA is similar as for other products at Amgen, therefore it is decided to always internalize final product assembly, even if the drug substance and drug product manufacturing are done externally.

6. **If building a new facility, use fixed equipment**

   Due to the extensive use of organic solvent, and because the current single-use equipment systems (e.g., storage bags, tanks, etc.) are not rated for fully organic systems, it is decided to assume the use of only fixed equipment if Amgen builds a new facility for siRNA drug substance manufacturing.

7. **If building a new facility, it will be based on the systems in Thousand Oaks**
   Based on engineering and design analysis of the potential new facility, the footprint fits an empty space in an existing building in Thousand Oaks. This will significantly decrease the capital investment as Amgen does not need to invest in a new building.

Figure 4-3 depicts the more detailed siRNA drug substance and drug product manufacturing process if Amgen chooses to do it internally.

Figure 4-3. Diagram of Manufacturing if Internalized

From there, "external" and "internal" definition are made, as well as the three scenarios to focus on for the analysis. Hereafter, term CMO will be used to refer to the outsourced vendor. This also provides a benchmark for cost analysis by fixing the geography.

As defined in Table 4-1, "external" means Amgen is outsourcing the DS and DP manufacturing, while keeping the FP process internal. On the other hand, "internal" means Amgen is taking all manufacturing step in-house, using new facility for DS and existing facilities for DP and FDP. There is currently no plan to outsource FDP, as Amgen's internal capability is perfectly aligned with what is required for siRNA.

Table 4-1. Definition of External and Internal

	Drug substance	**Drug product**	**Final drug product**
"External"	Outsourced vendor	Outsourced vendor	Amgen (existing)
"Internal"	Amgen (new)	Amgen (existing)	Amgen (existing)

Based on the definition of external and internal, three scenarios were developed to converge the focus of the business model and supply chain model analysis. In defining the scenarios, clinical and commercial processes were also differentiated. Clinical process refers to clinical phase trials manufacturing, with far less magnitude than commercial. Once the drug completes clinical trials, commercial manufacturing will start.

Here, the first scenario is where both clinical and commercial processes are outsourced. This is also referred to as the "baseline". The second scenario is where the clinical is outsourced, but when commercial phase is reached, the manufacturing is moved to internal in year-6, when the commercial manufacturing of Asset #1, if approved after the clinical trials, begins. The third scenario tries to internalize the manufacturing as soon as possible, which is in year-3. Thereafter, the manufacturing will be kept internal for commercial phase.

Table 4-2. Three Shortlisted, Most-feasible Scenarios for Analysis

	Clinical	**Commercial**
Scenario 1	External	External
Scenario 2	External	Internal (year-6)
Scenario 3	Internal (year-3)	Internal

Chapter 5

Supply Chain Model

The pandemic has exposed one of the major weaknesses of many supply chains: the inability to react to sudden, large-scale disruptions. An important way to start building supply chain resiliency is mapping the layers of suppliers, manufacturing plants, distributors, and other elements of the logistics network and applying a stress test to evaluate the ability to recover from the disruption of these sites. Once there is an understanding of where bottlenecks are located, various mitigation strategies can be considered upfront, including adding manufacturing capabilities or suppliers or creating buffer stocks.

5.1. Supply Chain Resilience Analysis

Traditional methods for managing supply chain risk rely on knowing the likelihood of occurrence and the magnitude of impact for every potential risk event that could materially disrupt a firm's operations. For common supply-chain disruptions – poor supplier performance, forecast errors, transportation breakdowns, and so on – those methods work very well, using historical data to quantify the level of risk.

However, it's a different story for low-probability, high-impact events – megadisasters like Hurricane Katrina in 2005, viral epidemics like the 2003 SARS outbreak, or major outages due to unforeseen events such as factory fires and political upheavals. Because historical data on these rare events are limited or nonexistent, their risk is hard to quantify using traditional models. As a result, many companies do not adequately prepare for them.

To address this challenge, Simchi-Levi et al. (2015) develop a model – a mathematical description of the supply chain that can be computerized – that focuses on the impact of potential failures at points along the supply chain (such as the shuttering of a supplier's factory or a flood at a distribution center), rather than the cause of the disruption. This type of analysis obviates the need to determine the probability that any specific risk will occur – a valid approach since the mitigation strategies for a disruption are equally effective regardless of what caused it. Using the model, companies can quantify what the financial and operational impacts would be if a critical supplier's facility were out of commission for, say, two weeks – whatever the reason. The computerized model can be updated easily and quickly, which is crucial since supply chains are in a continual state of flux.

A central feature of the model is time to recovery (TTR): the time it would take for a particular node (such as a supplier facility, a distribution center, or a transportation hub) to be restored to full functionality after a disruption. TTR values are determined by examining historical experience and surveying the firm's buyers or suppliers.

The model integrates TTR data with information on multiple tiers of supplier relationships, bill-of-material information, operational and financial measures, in-transit and on-site inventory levels, and demand forecasts for each product. Firms can represent their entire supply network at any level of detail—from individual parts to aggregations based on part category, supplier, geography, or product line. This allows managers to drill down into greater detail as needed and identify previously unrecognized dependencies. The model

can account for disruptions of varying severity by running scenarios using TTRs of different durations.

To conduct the analysis, the model removes one node at a time from the supply network for the duration of the TTR. It then determines the supply chain response that would minimize the performance impact of the disruption at that node – for instance, drawing down inventory, shifting production, expediting transportation, or reallocating resources. On the basis of the optimal response, it generates a financial or operational performance impact (PI) for the node. A company can choose different measures of PI: lost units of production, revenue, or profit margin, for instance. The model analyzes all nodes in the network, assigning a PI to each. The node with the largest PI (in lost sales, for instance, or lost units of production) is assigned a risk exposure index (REI) score of 1.0. All other nodes' REI scores are indexed relative to this value (a node whose disruption would cause the least impact receives a value close to zero). The indexed scores allow the firm to identify at a glance the nodes that should get the most attention from risk managers.

At its core, the model uses a common mathematical technique – linear optimization – to determine the best response to a node's being disrupted for the duration of its TTR. The model accounts for existing and alternative sources of supply, transportation, inventory of finished goods, work in progress and raw material, and production dependencies within the supply chain.

This approach provides several benefits as discussed below.

1. **It identifies hidden exposures**

   The model helps managers identify which nodes in the network create the greatest risk exposure – often highlighting previously hidden or overlooked areas of high risk. It also allows the firm to compare the costs and benefits of various alternatives for mitigating impact.

2. **It avoids the need for predictions about rare events**

   The model determines the optimal response to any disruption that might occur within the supply network, regardless of the cause. Rather than trying to quantify the likelihood that a low-probability, high-risk event will strike, firms can focus on identifying the most important exposures and putting in place risk management strategies to mitigate them.

3. **It reveals supply chain dependencies and bottlenecks**

   Companies can also use the analyses to make inventory and sourcing decisions that increase the robustness of the network. This includes taking into account the likely scramble among rival companies to lock in alternative sources if a supplier's disruption affects several firms. Such cross-firm effects of a crisis are often overlooked. Contracts with backup suppliers can be negotiated to give a company priority over others should a disruption with the primary supplier occur, which will decrease time to recovery and the financial impact.

4. **It promotes discussion and learning**

   In the course of analyzing the supply chain with this approach, managers engage in discussions with suppliers and internal groups about acceptable levels of TTR for critical facilities and share insights about best-practice processes to reduce recovery time. As a result, the impact of disruptions is minimized.

5.2. Supply Chain Model Structure

To start this off, an understanding of the supply chain flow is a must. In a simplified way, in this project the supply chain structure is defined in Figure 5-1. Two different setups are made: "internal" and "external", based on what have been defined in the previous chapter. An important note in this structure and analysis is that, since Amgen's siRNA

product has not been launched or manufactured commercially, there has not been a specific, robust structure of the supply chain for the siRNA modality. Therefore, a general structure and inventory level are used for this analysis. Some assumptions are also made, such as the number of warehouses, the location of the warehouses, etc.

Looking at Figure 5-1, in the "internal" setup, the supply chain starts with raw material vendors, which supply to the DS manufacturing plant. The finished DS products will be stored in a DS warehouse in a different location as the DS plant. Then, it will be moved to the DP manufacturing plant. Again, the finished DP products are stored in two different DP warehouses located separately from the plant. The DP products will be then transported to the FDP manufacturing plant to be processed into final products, and the final products will be stored in the FDP warehouse. The end-node of this process is customer as the receiver of the final product.

Conversely, for the "external" setup, based on the definition introduced in the previous chapter, the CMO will take over the DS and DP manufacturing processes, and supply Amgen with the finished DP products. Therefore, in the supply chain model, the CMO will directly connect to the DP warehouse, and after that the process will be the same as in the "internal" setup. Amgen does not have visibility into the CMO's inventory setup, but there is a minimum inventory level specified in the contract with the CMO for the finished DP products.

Note that in this case, it is assumed to use one of everything – DS plant, DS warehouse, DP plant, DP warehouse, etc. – but for DP and FDP, Amgen has backups for both plants and warehouses, as Amgen can utilize more than one existing DP and FDP plants and warehouses. Therefore, when the primary DP or FDP plant or warehouse is down/off, Amgen can use a backup plant or warehouse instead of needing to build a new one from scratch. Meanwhile, for DS, the current plan is to have only one plant and one warehouse, both in Amgen's sites. Therefore, there is no back-up site for the DS plant or warehouse.

The values related to TTR and inventory level for a curated supply chain setup for a specific modality or product are usually available only one or two years before commercialization. Hence, for this analysis an average or general value are determined, derived from interviews with multiple stakeholders, different modality teams for various products, and historical data. From there, for the "internal" setup it is agreed to have inventory levels in DS, DP, and FDP warehouses as seven months, six months, and three months of supply, respectively. Meanwhile, in the "external" setup the values are higher since Amgen will bear more risks, with the DP warehouse holding eight months of inventory and the FDP warehouse holding five months of inventory, i.e., the DP and FDP inventory levels in the "external" setup are two months larger than in the "internal" setup. It is assumed that the TTR for the DS manufacturing plant is nine months, since it has no back-up and a new plant needs to be rebuilt. Meanwhile, for DP and FDP, when the primary site is down, it is assumed that the currently non-utilized capacity in the other plants can be used, therefore only taking three months of TTR to do tech transfer and manage the logistics.

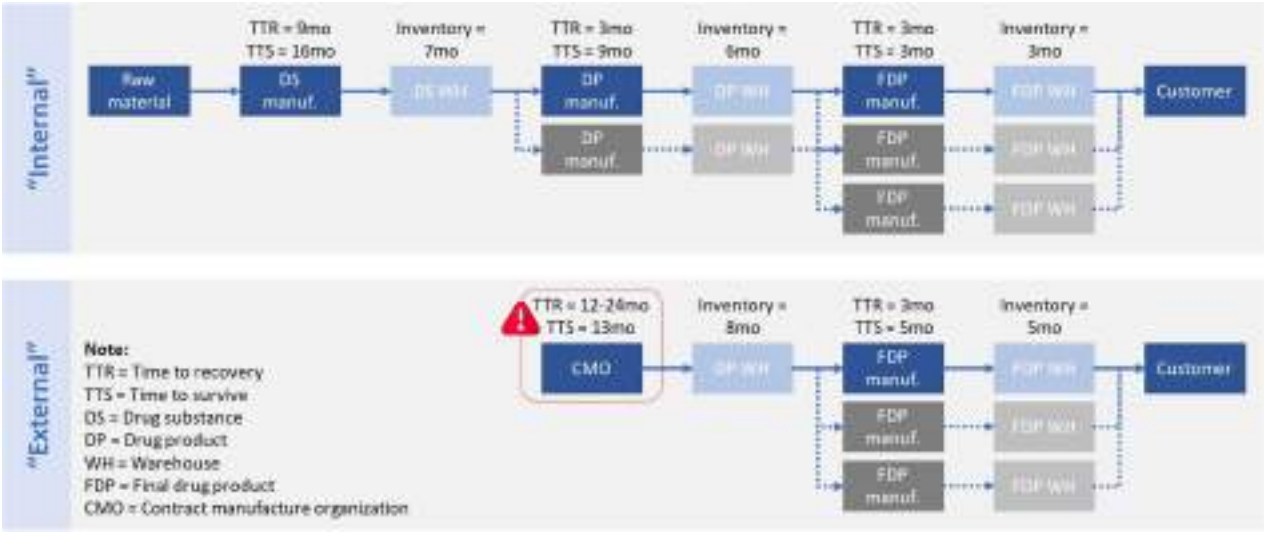

Figure 5-1. Supply Chain Resilience Analysis

5.3. Discussion on Supply Chain Model

Based on the structure of the supply chain, there are five nodes: raw materials, DS manufacturing, DP manufacturing, FDP manufacturing, and customer. The warehouses – DS warehouses, DP warehouses, and FDP warehouses – are located relatively away from the manufacturing sites and will be used in the model as the inventory backup for when a node is disrupted. For example, when FDP manufacturing node/facility is disrupted, Amgen will still have an undisrupted FDP warehouse with several months of inventory to keep the supply chain running.

Two key important factors in the model developed by Simchi-Levi et al. (2015) as explained above are TTR and time-to-survive (TTS). In this project, TTR is the time it would take for a particular node to be restored to full functionality after a major disaster, such as hurricane. TTR data is obtained by conducting interviews and looking at historical data. Meanwhile, TTS, meaning the length of time the supply chain can still be running when a node is off, is calculated by adding the inventory levels of the steps after the disrupted node. For example, when FDP manufacturing is off, the TTS is the inventory level of FDP warehouse inventory; when DP manufacturing is off, the TTS is the sum of the inventory levels in the DP warehouse and the FDP warehouse; and so on. This is because, for example, when DP manufacturing is off, even though FDP is still running, there is no additional DP product beyond the ones in the DP warehouse to be processed in the FDP warehouse, therefore the number of months it will survive is the DP warehouse inventory level, plus the FDP warehouse inventory (the finished products already there).

As explained by Simchi-Levi et al. (2015), the supply chain is resilient when TTR is less than TTS in each node. This means, the supply chain will have more time to run without the particular node than the time needed to recover that node – the supply chain can survive and keep running while waiting for that node to be recovered. From Figure 5-1, in the "internal" scenario, TTR is always less than TTS for all nodes, which means that the "internal" supply chain is resilient. However, when considering the "external" supply

chain, the CMO node is worrisome. Even though for the inventory level in the "external" setup is more than the "internal" setup to strengthen the supply chain, there is a huge variability on the TTR in the CMO node. In this case, the CMO may suddenly no longer be able to supply Amgen with the raw materials, and Amgen will need to find another vendor. Finding an alternative vendor typically takes 12 to 24 months, as there will be a lot of administrative and regulative steps, as well as tech transfer. This is a huge variability. While the lower-end TTR (12 months) is shorter than the node's TTS (13 months), the "worst-case scenario" has a TTR of 24 months, which makes the CMO a weak link in the "external" supply chain setup.

Knowing that the CMO in the "external" supply chain setup is the weak link, there are two ways to account for this in the business model. The first one is to increase the inventory level to reach a TTS of 24 months for the CMO node. The second option is to have a back-up DS and DP CMO that works together and supplies a minimum amount of DP materials to Amgen, just to keep it online in Amgen's system, so that if the primary CMO goes off, Amgen can quickly switch to the secondary CMO. Since the secondary CMO has been running all the time for Amgen, it does not need additional time to setup as is needed to find a CMO from scratch. In this project, it is decided to use the second option, since the inventory level calculation of the asset is not yet robust given its immaturity (still in development and planned to launch only in year-8), and Amgen has used secondary CMOs before.

Implementing this option to the business model, there will be an additional line item of cost in the "external" setup, to consider the additional cost of keeping a secondary or back-up CMO online in the supply chain.

An important next step to this supply chain analysis is to curate a specific supply chain setup in terms of numbers of warehouses, location of the warehouses, and the inventory level at each step, instead of using the current general values. In defining the final setup of the supply chain when it is close to the launch date in year-8, this supply

chain resilience analysis should also be performed, and the existing takeaways that the CMO might be the weak link in the "external" setup must be carefully considered.

Chapter 6

Business Model

A business model is created to analyze the Present Value of Expense (PV of Expense) for each scenario defined in Chapter 4, Table 4-2. It is decided to use PV of Expense instead of NPV because this analysis is only looking at the operations side, not including non-operations financials (e.g., marketing cost, etc.). Out of the three shortlisted scenarios, the revenue will stay the same as the differentiation between the scenarios are on the cost side. Therefore, the PV of Expense will be compared to identify the lowest cost over the span of 20 years (year-0 to year-19). The reason why 20 years timespan is chosen is to capture the entire duration of Asset #1's commercialization from launch until its peak.

6.1. Business Model Cost and Revenue Items

The cost and revenue items included in the business model are summarized in Table 6-1. The tick marks in the table below indicate that the items are included in the model for each scenario. The black tick marks indicate fixed decisions parameters. The orange tick marks indicate variable or sensitivity input, which is the volume sold. The blue tick marks indicate optimized parameters, for example the equipment cost. Costs are modeled based on best guesses from past expenses.

Table 6-1. Business Model Cost and Revenue Items

Cost/Rev. Group	Cost/Rev. Item	Scenario 1	Scenario 2	Scenario 3
Revenue	Volume sold	✓	✓	✓
	Price	✓	✓	✓
Cost of Goods Sold	CMO Bills	✓	✓*	✓*
	Manufacturing FTE		✓	✓
	Manufacturing OSE		✓	✓
	Raw materials		✓	✓
	Consumables		✓	✓
	Manuf. overheads		✓	✓
	Lumpsum internal	✓**	✓**	✓**
Operating Expenses	Development FTE	✓	✓***	✓***
	Development OSE	✓	✓***	✓***
Tech. Transfers	One-time transfer	✓	✓	✓
Capital Expenditures	Building		✓	✓
	Equipment		✓	✓

Note: FTE stands for full-time equivalent, or human resources; OSE stands for other expenses related to human resources, for example travel expenses.
* CMO bills will stop at the end of year-6 for Scenario 2 and year-3 for Scenario 3, which are the last year of externalization, respectively. Afterwards the manufacturing process (DS and DP) will be internalized.
** "Lumpsum internal" cost includes DP and FDP internal costs that cannot be broken down into raw materials, consumables, etc., therefore going into this bucket. For all scenarios, this includes FDP internal cost, while for Scenarios 2 and 3, this includes DP and FDP internal costs.
*** Development cost FTE and OSE are slightly higher in Scenarios 2 and 3 where there is an internalization process. The differentiation comes from an incremental cost for analytics development for the internalization.

Next, the components of the business model from Table 6-1 will be explained.

Volume sold and price

There are two types of markets for Asset #1: market A and market B. Market A is tapped from the very beginning of the commercialization process, while market B will be tapped relatively later. Since Asset #1's commercialization will only start in a future date, the demand projection has low confidence level, therefore three demand scenarios are considered for the analysis:

- **High-demand scenario** reaches 40% market for both market A (by year-15) and market B (by year-18)
- **Mid-demand scenario** reaches 40% market for market A (by year-15), and 10% for market B (by year-18)
- **Low-demand scenario** reaches 40% market for market A (by year-18)

The demand projections for the three scenarios are illustrated in Figure 6-1 and the details are presented in Appendix A. It is emphasized that the differentiation of the three demand scenarios will start in around year-12/year-13, when Amgen starts tapping market B. Before then, the three demand scenarios have the same projections, as only market A is tapped, and there is no difference in the three demand scenarios before market B is penetrated.

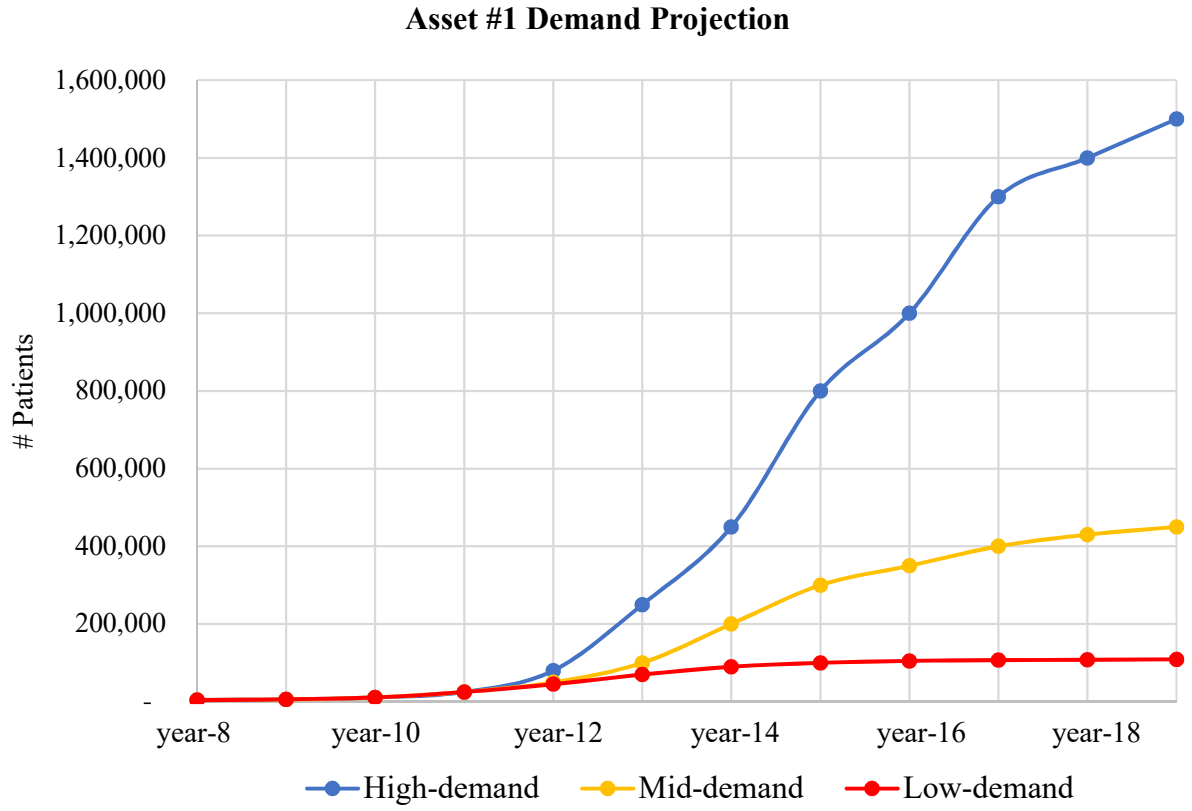

Figure 6-1. Demand Projection of Asset #1

Manufacturing FTE, OSE, and capital expenditures

Figure 6-2 presents the layout of the minimum-capacity facility which serves as the baseline. Amgen Engineering Team proposed this facility design for use in this model. There are multiple ways to increase capacity: adding a tangential flow filtration (TFF) into a suite (from one TFF to two TFFs), adding another suite, or changing the 24x5 operations to 24x7. Using Amgen's capacity modeling tool, Amgen's Capacity Planning Team came up with the capacity progression data in Figure 6-3. On the left-most side, the baseline, or the lowest, capacity is 36 kg/year with 1:1 production (85 cm sense-strand (SS) column and 50 cm antisense-strand (AS) column), corresponding to the facility layout in Figure 6-2. To add capacity, for example, adding one TFF into that layout will increase

the capacity to 51 kg/year, while changing the operations into 24x7 will reach 72 kg/year. Furthermore, doing both will increase the capacity to 89 kg/year. Another way is to change the AS column size into 85 cm to reach 54 kg/year. For each facility setup there is a respective capital cost, as well as manufacturing FTE and OSE costs. For example, Amgen will need more capital to get more TFF and to have a bigger column, and 24x5 setup will incur lower manufacturing FTE costs compared to 24x7 setup.

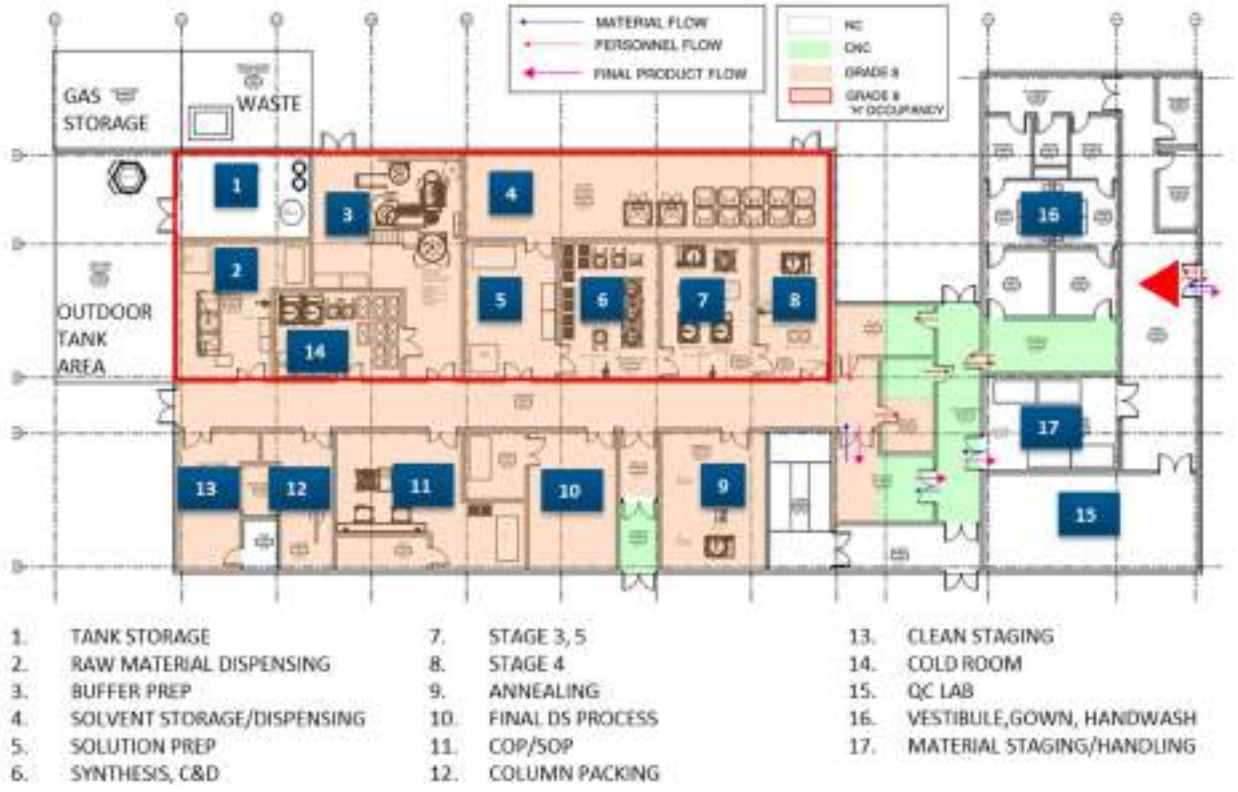

Figure 6-2. Minimum Facility Setup for the Lowest Capacity

To have an additional suite, Amgen would need to add the part highlighted in orange in Figure 6-2, which would incur around 60% of the total building capital costs. The orange highlighted part does not include areas such as gowning and QC laboratory, which do not need to be duplicated if Amgen build another suite.

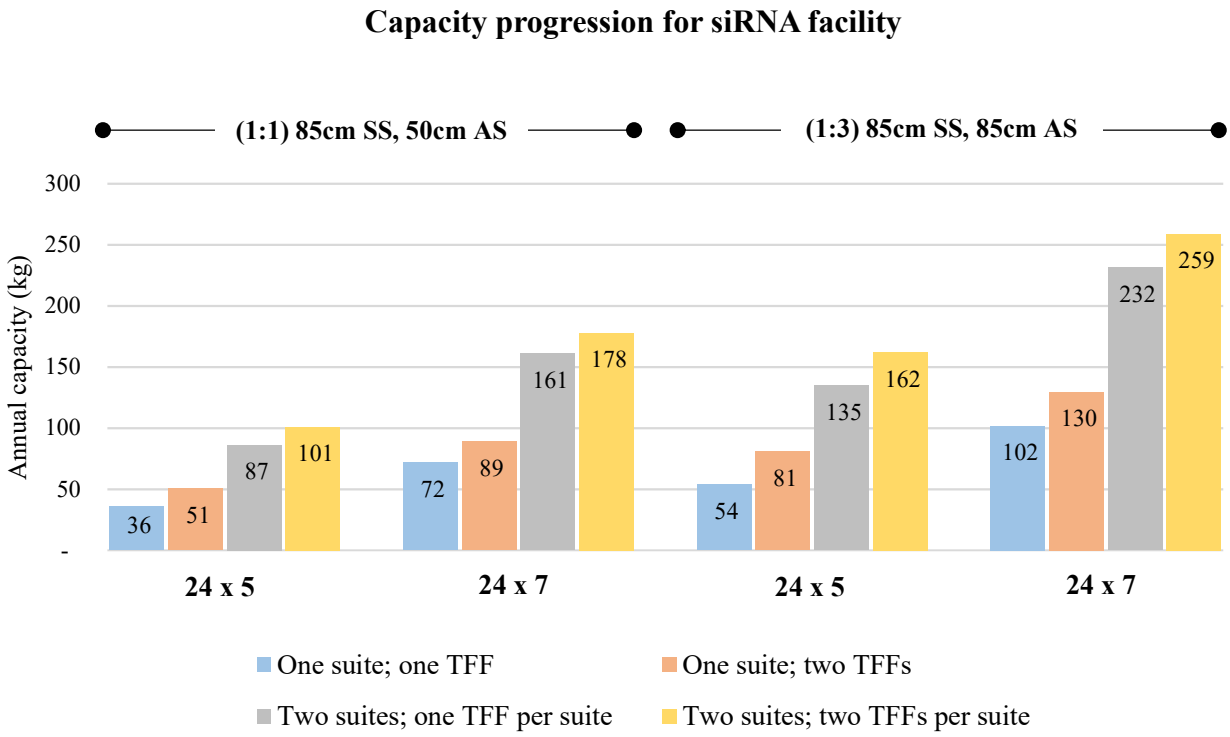

Figure 6-3. Capacity Progression for siRNA Facility

Because there are many ways to increase capacity, a mixed integer optimization in Chapter 6.3 is used to identify the best option for capacity progression that requires the least expense.

CMO bills and one-time development costs

CMO bills and one-time development costs come from Amgen's current CMO quotes regarding the price per gram DS and price per vial DP with the projected demand level, both for clinical and commercial phases. One-time development costs incurred by the CMO, such as purchasing a new resin column with a different size, and technology transfer will be absorbed by Amgen as well.

Raw materials and consumables

The volumes required by both raw materials and consumables are extracted from historical reports of Amgen's CMO who has produced the DS before. The big bucket of the raw materials, adding up to 80% of the total costs, are the amidites (Guanine, Adenine, Cytosine, and Uracil) and the directing ligand (DL). Therefore, for these materials, Amgen obtains a very recent quote from a vendor to have a good estimate of the current price points. For the rest of the raw materials and consumables, their price points in Amgen's database is used. Additionally, for the items not listed in the database, quotes from vendors are requested for the input.

Manufacturing overheads and lumpsum internal costs

Internal commercialization price for FDP and DP cannot be broken down into granular cost items (e.g., raw materials, FTE, etc.), but Amgen has the average cost per vial based on historical data and the location of the facility. Because it is not known yet where Asset #1 is going to be produced, the average cost per vial of the facilities for FDP and DP internal commercialization is used.

For manufacturing overheads, the common practice is to look at how much water or electricity, as well as other shared resources (e.g., building manager, security, etc.) is spared for Asset #1's manufacturing in the existing site. However, again, since this does not exist yet, a deep dive on this cost item cannot be done, therefore it is assumed that the manufacturing overheads to be equal to the manufacturing FTE costs, as it is typically the case from historical data.

Operating expenses (process development)

Process development cost is the expenses before the launch, related to developing the process and analytics of Asset #1. The working groups related to this are: DS, DP, FDP, AS (analytics), and XPD (outsourcing or external relations, for example with vendors and

CMO). Interviews and workshops are carried out with the groups to understand how much FTE and OSE costs related to Asset #1's process development is needed until its launch in year-8. From these discussions, it is understood that AS group will have an additional cost if Amgen internalize the process, while for the other groups the costs will be the same whether the manufacturing is internal or external.

Depreciation and other costs

Depreciation is calculated with a linear method, 10 years for equipment (non-building) and 40 years for building. Discount rate is assumed to be 8%, used for calculating the present value.

6.2. Mixed Integer Programming

Linear programming maximizes (or minimizes) a linear objective function subject to one or more linear constraints. The technique finds broad use in operations research. A mixed-integer programming (MIP) problem is one where some of the decision variables are constrained to be integer values (i.e., whole numbers such as -1, 0, 1, 2, etc.) at the optimal solution.

Typically, the form of mixed integer programming (MIP) problem is as follows:

Objective:	minimize $c^T x$
Constraints:	$Ax = b$ (linear constraints)
	$l \leq x \leq u$ (bound constraints)
	Some or all x_j must take integer values (integrality constraints)

The integrality constraints allow MIP models to capture the discrete nature of some decisions. For example, a variable whose values are restricted to 0 or 1, called a binary

variable, can be used to decide whether or not some action is taken, such as building a warehouse or purchasing a new machine.

Another type of commonly used MIP is models with a quadratic objective and/or quadratic constraints:

Objective:	minimize $x^T Q x + q^T x$
Constraints:	$Ax = b$ (linear constraints)
	$l \leq x \leq u$ (bound constraints)
	$x^T Q_i x + q_i{}^T x \leq b_i$ (quadratic constraints)
	Some or all x_j must take integer values (integrality constraints)

MIP models with a quadratic objective but without quadratic constraints are called Mixed Integer Quadratic Programming (MIQP) problems. MIP models with quadratic constraints are called Mixed Integer Quadratically Constrained Programming (MIQCP) problems. Models without any quadratic features are often referred to as Mixed Integer Linear Programming (MILP) problems.

6.3. Optimization on Capacity Progression

To optimize the capacity progression, a mixed integer program with Excel Solver function is used. Since know the different setups' capacity, capital investment, labor FTE cost, and OSE cost are known, a mixed integer program can be developed to identify which capacity progression option is the most cost-effective while still fulfilling the volume required for each year. Amgen internally enforces a threshold utilization of 80%; that is, the volume needed cannot exceed 80% of the total capacity. The analysis starts from year-3, because the earliest year to build the facility is year-0, and it will take three years for it to be ready-to-run (year-3).

The objective function of this mixed integer program is to minimize the PV of expense from year-0 to year-19. The first constraint is to determine the number of facility type per year. x indicates the facility setup in Figure 6-3. There are 16 facility setups, numbered from left to right in Table 6-3: $x = 1$ is the facility setup with the capacity of 36 kg/year, $x = 2$ is the facility setup with the capacity of 51 kg/year, $x = 3$ is the facility setup with the capacity of 87 kg/year, etc. t is the year. Therefore, for example this: $x_t = 5_{year\,4} = 1$, means in year-4, one facility setup with the capacity of 72 kg/year (1:1 production (85 cm sense-strand (SS) column and 50 cm antisense-strand (AS) column) for 24x7) will be needed.

The second constraint is to ensure that the volume of product needed in a year is less than or equal to 80% of the capacity available in that year to allow maintenance and operation buffer. On the left-hand side of the constraint, $Vol.needed_t$ is the demand per year. On the right-hand side of the constraint, the total capacity in a year is determined by multiplying the number of facility setup (x_t) with the capacity of the facility setup itself ($Capacity_x$) for the 16 setups, and adding them all. For example, in $t = year\,3$ the plant will need only one facility setup number one, or $x_t = 1_{year\,3} = 1$. Therefore, the rest, $x_t = 2_{year\,3} = 0$, $x_t = 3_{year\,3} = 0$, until $x_t = 16_{year\,3} = 0$. For facility setup number one, the capacity is 36 kg/year, thus $Capacity_x = Capacity_1 = 36\,kg/year$. Multiplying each x_t with $Capacity_x$ from $x = 1$ to $x = 16$ in $t = year\,3$, since for $x = 2$ up to $x = 16$, the $x_{year\,3}$ is always zero, the total capacity will be $x_t = 1_{year\,3} = 1$ times $Capacity_x = Capacity_1 = 36\,kg/year$, which is 36 kg/year. Then, it is multiplied by 80% to ensure the threshold utilization.

The third constraint is used to determine the capital cost for each year. The concept is similar to the second constraint, but instead of $Capacity_x$, in the third constraint x_t is multiplied by $Capital_x$, the capital cost for each facility setup. The total capital for each year is the sum of the multiplication of x_t and $Capital_x$ for each facility setup x.

The fourth and fifth constraints are related to CMO bills. In the fourth constraint, if there are one or more facility setups, then the CMO bill is zero, because Amgen will not be using them anymore as Amgen will be manufacturing in-house. The non-CMO costs are positive, according to the calculation in the business model (raw materials, consumables, etc.). In the fifth constraint, if there is no facility, then the CMO bill is the multiplication of demand in the year and the CMO price per kg. The non-CMO costs are hence zero because there is no manufacturing in-house.

The two last constraints are equations to calculate non-capital costs and PV of expense per year, respectively. Non-capital costs consist of CMO bills and everything other than it. PV of expense consists of capital costs and non-capital costs for the year.

$$\text{Min} \sum_{t=year\ 0}^{year\ 19} PV\ of\ Expense_t$$

$s.t.$: $x_t \in integer$ $\quad x = 1, \dots, 16\ (Facility\ setup)$; $t = year\ 3, \dots, year\ 19\ (Year)$

$$Vol.needed_t \leq 80\% \sum_{x=1}^{16} x_t\ Capacity_x \quad for\ each\ t$$

$$Capital_t = \sum_{x=1}^{16} x_t\ Capital_x \quad for\ each\ t$$

$$If \sum_{x=1}^{16} x_t \geq 0, then\ CMO_t = 0, and, Non\ CMO_t \geq 0$$

$$If \sum_{x=1}^{16} x_t = 0, then\ CMO_t = Vol.needed_t \times CMO\ price/kg, and, Non\ CMO_t = 0$$

$$Non\ capital\ costs_t = CMO_t + Non\ CMO_t$$

$$PV\ of\ Expense_t = Non\ capital\ costs_t + Capital_t$$

The example result of this optimization program is in Table 6-2. On the left-hand side, there are 16 facility setups' capacity, based on Figure 6-3. The integer numbers on the right-hand side of the 16 facility setups are the x_t. In this result, the required facility in year-6 is the smallest setup – one suite, one TFF, 1:1, 24x5 operations. This is sufficient for seven years, and then in year-13 to year-14, facility setup number 16 is required – two suites, four TFFs, 1:3, 24x7. In year-15, on top of facility number 16, another one suite, two TFFs, 1:1, 24x5 is required, resulting in three suites, with two TFFs each suite, and two suites 1:3, 24x7 while the other one suite operating 1:1, 24x5. In year-16, the latter suite needs to be upgraded into 1:3, 24x7. In year-17, an additional one suite is required, taking one TFF from the newer suite, resulting in four suites, two of them having two TFFs each, and two having only one TFF each (total six TFFs), all operate 1:3 and 24x7. In year-18, the latter two suites need additional one TFF each, resulting in four suites with two TFFs each, 1:3, 24x7. On top of that, an additional suite with the smallest setup is required in year-18. In year-19, two TFFs in each of the five suites are required, four of which operate in 1:3, 24x7 operations and one in 1:1, 24x5. This optimized capacity progression is laid out in Table 6-3.

Table 6-2. Capacity Progression Optimization (High Demand Level, Scenario 2)

Scenario #2															
Financials projection															
		year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Operations (only for internal new sites)															
Capacity progression details															
Maximum capacity	kg	57.60	57.60	57.60	57.60	57.60	57.60	57.60	414.40	414.40	495.20	621.60	784.80	886.40	909.60
Checking suite numbers	Int.	1	1	1	1	1	1	1	1	1	2	2	2	3	3
16	Int.	1	1	1	1	1	1	1	-	-	-	-	-	1	-
15	Int.	-	-	-	-	-	-	-	-	-	1	-	-	-	1
87	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
136	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
72	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
89	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
161	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
178	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
54	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
81	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
134	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
152	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
102	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
139	Int.	-	-	-	-	-	-	-	-	-	-	1	-	-	-
232	Int.	-	-	-	-	-	-	-	-	-	-	-	1	-	-
259	Int.	-	-	-	-	-	-	-	1	1	1	1	1	2	2

Table 6-3. Capacity Progression Summary (High Demand Level, Scenario 2)

	Yr-6-12	**Yr-13-14**	**Yr-15**	**Yr-16**	**Yr-17**	**Yr-18**	**Yr-19**
Suite A	1 TFF, 1:1, 24x5	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7
Suite B	-	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7
Suite C	-	-	2 TFF, 1:1, 24x5	2 TFF, 1:3, 24x7	1 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7
Suite D	-	-	-	-	1 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7
Suite E	-	-	-	-	-	1 TFF, 1:1, 24x5	2 TFF, 1:1, 24x5

6.4. Optimization Beyond the Predefined Scenarios

In the predefined scenarios, internalization is considered to start in year-3 or year-6. However, it could be possible that starting internalization in a different year may result in a lower PV of Expense than the predefined scenarios. In this chapter, a mixed integer program will help analyze whether such a situation may arise. Similar to Chapter 6.3, mixed integer programming is created for the analysis.

The first half of the program is the same as Chapter 6.3, until the third constraint. The fourth constraint indicates that the non-CMO costs are positive, based on the calculation in the business model (raw materials, consumables, etc.). The fifth constraint is an equation to calculate CMO costs, which is the multiplication of demand and CMO price per kg.

Then, a new binary variable, y, is introduced, indicating internal or external. If $y = 1$, it means internal, and if $y = 0$, it means external. This is translated into the sixth constraint, $y_t \in \{1, 0\}$. The seventh constraint is created to make sure that y_{t+1} cannot be lower than y_t, which means once the manufacturing is internalized, Amgen cannot go back to outsourcing it.

The eighth constraint is made to determine whether the optimal capital cost is zero (not building the facility) or positive (based on the result from the third constraint), which then will relate to the ninth and tenth constraints. The ninth constraint is made to calculate non-capital costs. If $y_t = 0$, $|y_t - 1| = 1$, and it is multiplied with CMO costs. This will result in a positive CMO costs value, which is aligned with the definition of outsourcing ($y_t = 0$). On the other hand, the non-CMO costs are multiplied by y_t, resulting in zero. If $y_t = 1$, $|y_t - 1| = 0$. Multiplying this with CMO costs, results in zero CMO costs, which is aligned with the definition of in-house manufacturing ($y_t = 1$). In this case, the non-CMO costs are multiplied by $y_t = 1$, resulting in a positive value based on the calculation in the fourth constraint. The last constraint is an equation to calculate the PV of expense per year. PV of expense consists of capital costs and non-capital costs for the year.

$$Min \sum_{t=year\ 0}^{year\ 19} PV\ of\ Expense_t$$

$s.t.$: $x_t \in integer$ $\quad x = 1, \dots, 16\ (Facility\ setup)$

$t = year\ 3, \dots, year\ 19\ (Year)$

$$Vol.needed_t \leq 80\% \sum_{x=1}^{16} x_t\, Capacity_x \qquad for\ each\ t$$

$$Capital_t = \sum_{x=1}^{16} x_t\, Capital_x \qquad for\ each\ t$$

$$Non\ CMO_t \geq 0$$

$$CMO_t = Vol.needed_t \times CMO\ price/kg$$

$y_t \in \{1, 0\}$ $\quad t = year\ 3, \dots, year\ 19\ (Year)$

$$y_t \geq y_{t-1}$$

$$Optm.capital_t = y_t Capital_t$$

$$Non\ capital\ costs_t = |y_t - 1| CMO_t + y_t Non\ CMO_t$$

$$PV\ of\ Expense_t = Non\ capital\ costs_t + Optm.capital_t$$

The example result of this program is in Table 6-4. This is very similar to Table 6-2, but there is an additional last row, "Yes/No" in the table. This is the binary variable y. Based on this result, the most optimized year to start internalization is in year-13. Even though in the year before year-13, there are results on the facility setup, it will be multiplied by $y = 0$ (or "-" in the table below), resulting in zero facility, which means outsourcing.

Table 6-4. Scenario Optimization (High Demand Level)

Optimized Scenario															
Financials projection															
		year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Operations (only for internal new sites)															
Capacity progression details															
Maximum capacity	kg	57.60	57.60	57.60	57.60	57.60	57.60	57.60	414.40	414.40	495.20	621.60	784.80	886.40	909.60
Checking suite numbers	Int.	1	1	1	1	1	1	1	1	1	2	2	2	3	3
[redacted]	Int.	1	1	1	1	1	1	1	-	-	-	-	-	1	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	1	-	-	-	1
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	1	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	1	-	-
[redacted]	Int.	-	-	-	-	-	-	-	1	1	1	1	1	2	2
Yes/No	Bin.	-	-	-	-	-	-	-	1	1	1	1	1	1	1

Table 6-4. Scenario Optimization Summary (High Demand Level)

	Yr-6-12	**Yr-13-14**	**Yr-15**	**Yr-16**	**Yr-17**	**Yr-18**	**Yr-19**
Suite A	-	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7
Suite B	-	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7
Suite C	-	-	2 TFF, 1:1, 24x5	2 TFF, 1:3, 24x7	1 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7
Suite D	-	-	-	-	1 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7	2 TFF, 1:3, 24x7
Suite E	-	-	-	-	-	1 TFF, 1:1, 24x5	2 TFF, 1:1, 24x5

6.5. Discussion on the Business Model

The details of the business model and the results for the three predefined scenarios (see Table 4-2) as well as for the optimized scenario (see Chapter 6.4) are presented in Appendix B. As seen in Table B-2 and Table B-3, the results show that it will not make sense to internalize if the demand level is medium or low. When the demand level is medium or low, the PV of Expense under full externalization (Scenario 1) is always lower than that under Scenario 2 or Scenario 3. This conclusion is corroborated by the fact that the optimized scenario determined by the mixed integer program is indeed full externalization.

Conversely, when the projected demand is high (Table B-1), Scenario 2 and Scenario 3 have a lower PV of Expense than Scenario 1, which in the criteria means that internalizing in year-3 or year-6 is more desirable than full externalization. However, the mixed integer program shows that another scenario beyond the three predefined ones would yield **the lowest PV of Expense under the high-demand scenario: internalizing in year-13**. This result implies that Amgen needs to start building the facility in year-10, because it takes three years to build a facility from construction until it is ready to run. Looking back into Figure 6-1 on the demand projection, year-10 is only two years after commercialization launch (year-8), when the demand trend is still immature. More specifically, Figure 6-1 shows that the differentiation between the high, medium, and low-demand scenarios will only become evident when Amgen starts tapping into market B in year-12 or year-13. Therefore, **in year-10 there still exists a great deal of uncertainty regarding whether Asset #1's demand level would be high, medium, or low**, creating a high level of risk for Amgen if the company builds the facility then.

To better understand the cost implication if Amgen waits until year-12 or year-13 to reassess the situation and decide whether to build a facility, the model is run multiple

times to evaluate the PV of Expense if we choose to internalize in year-15 or year-16. The results are summarized in Figure 6-4.

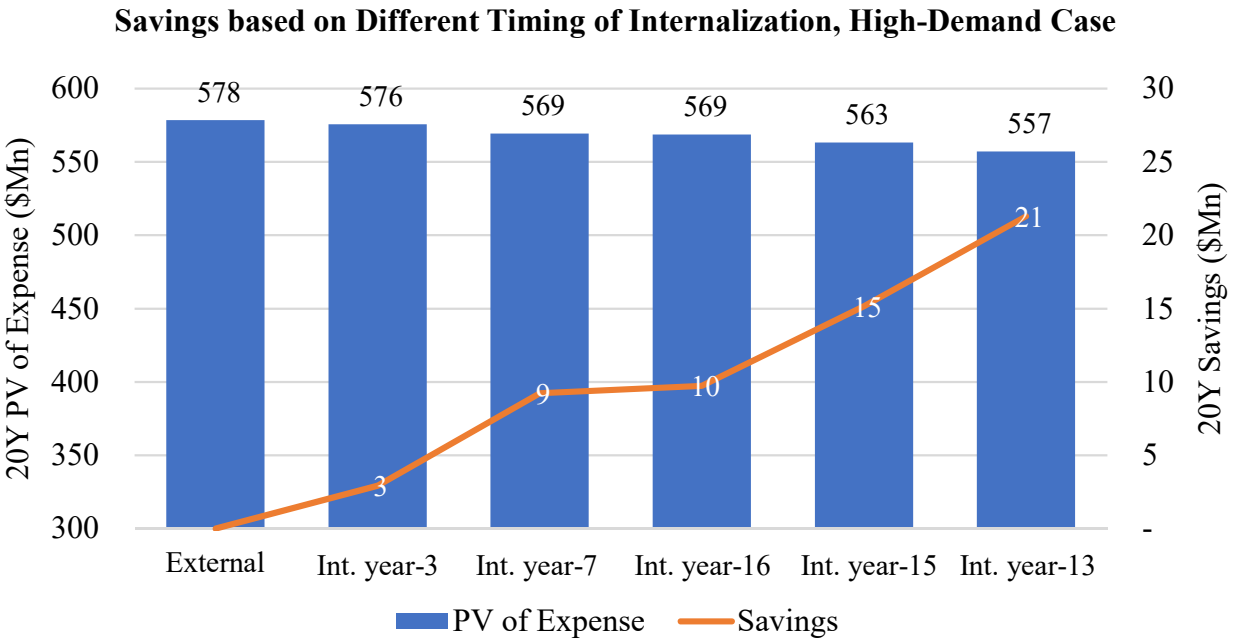

Figure 6-4. Savings Based on Different Timing of Internalization, High-demand Case

Even if the internalization starts in year-15 and year-16, Amgen will still achieve considerable savings, albeit lower than internalizing in year-13. However, by waiting until year-12 or year-13 to build the facility, Amgen can significantly improve its demand prediction, as Amgen has reached the inflection point in the demand model, therefore the final demand can be better predicted, and a better investment can be made, avoiding potentially substantial risk due to prediction errors. This is clearly preferred by Amgen, especially because the decision is highly affected by the siRNA volume sold and Amgen potentially plans to launch another siRNA asset or program later, which will add volume into the business model (which only captures Asset #1 right now). In that case, Amgen can potentially achieve more cost savings if Amgen chooses to internalize!

6.6. Sensitivity Analysis of Key Input Parameters

Three key input parameters that for the sensitivity analysis are: Amidites and DL costs, capital investment expense, and CMO price. The sensitivity analysis is applied for Scenario 3 (internalization in year-3) and Scenario 1. The reason why Scenario 2 (internalization in year-6) is not included in the sensitivity analysis is because its PV of expense is very similar to Scenario 3. One important assumption is that when a sensitivity analysis is done on one parameter, the rest of the parameters remain constant. The result of this sensitivity analysis is in Figure 6-5, Figure 6-6, and Figure 6-7. As can be seen, the parameter that has the strongest impact on the optimal PV of Expense is the CMO price. That is, a slight change in the CMO price will result in the largest change in the PV of Expense compared to the two other parameters. Thus, Amgen should monitor this parameter closely and make sure the value used as an input to the business model is accurate and recent.

An important takeaway from this sensitivity analysis is that changes in the key input parameters can alter the conclusion of whether Amgen should internalize or externalize siRNA production.

Amidites and directing ligand costs

As can be seen in Figure 6-5, under the high-demand case, internalizing results in a lower PV of Expense when the amidites and DL cost is 30%-100% of the current value. However, externalizing becomes the lower-expense option if the amidites and DL cost becomes higher than the current value. Meanwhile, for the low- and mid-demand cases, externalizing yields a lower expense at the current value of the amidites and DL cost. However, when this cost is reduced to lower than 80% (35%) of the current value for the mid-demand (low-demand) case, internalizing becomes the lower-expense option.

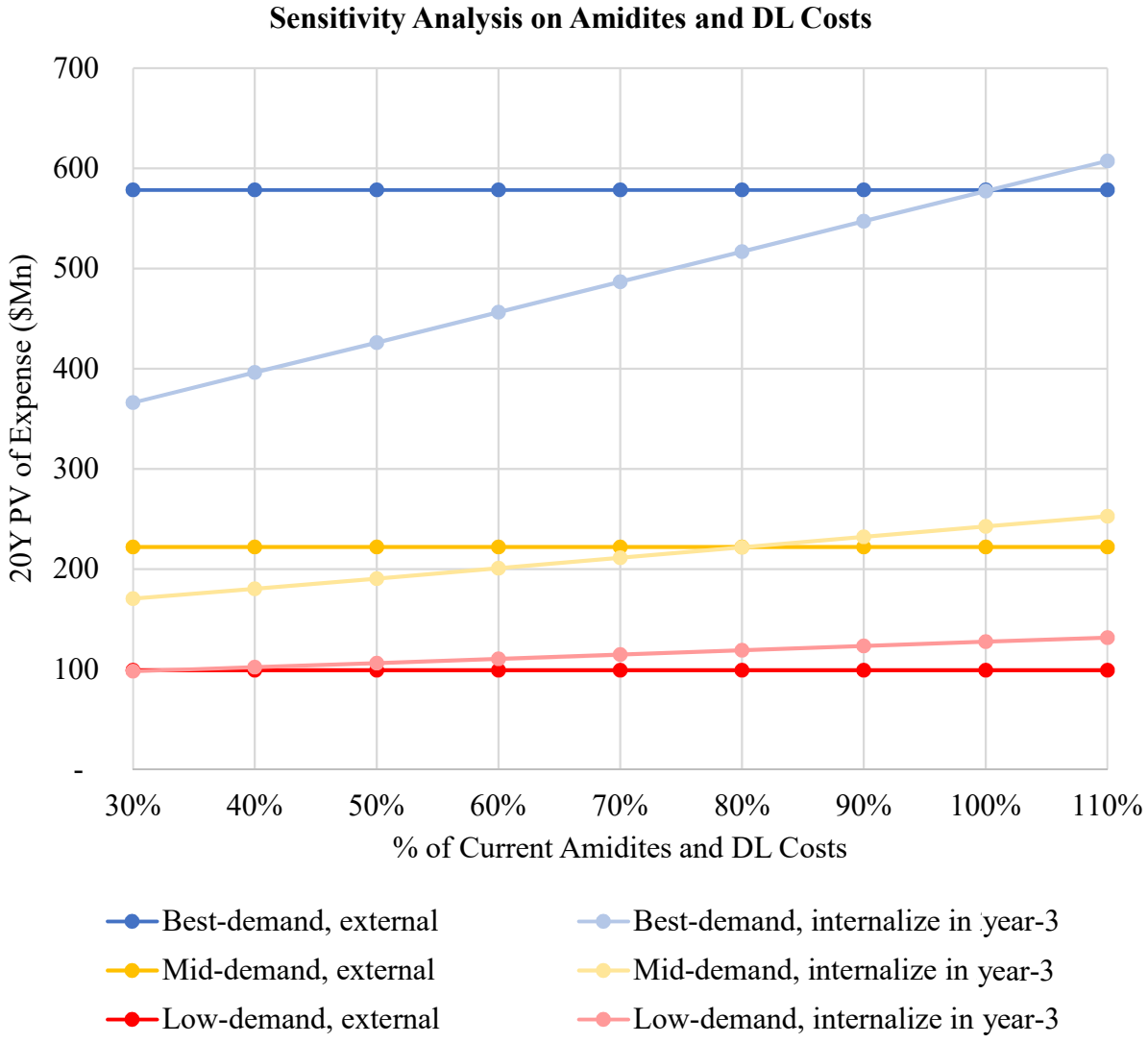

Figure 6-5. Sensitivity Analysis of Amidites and Directing Ligand Costs

Capital investment expense

The results for this parameter are very similar to the results for the amidites and DL cost parameter, but less sensitive. As can be seen in Figure 6-6, under the high-demand case, internalizing results in a lower PV of Expense when the capital investment is 10%-100% of the current value. However, externalizing becomes the lower-expense option if the capital investment becomes higher than the current value. Meanwhile, for the low- and mid-demand cases, externalizing yields a lower expense at the current value of the capital

investment. However, when this cost is reduced to lower than 60% (15%) of the current value for the mid-demand (low-demand) case, internalizing becomes the lower-expense option.

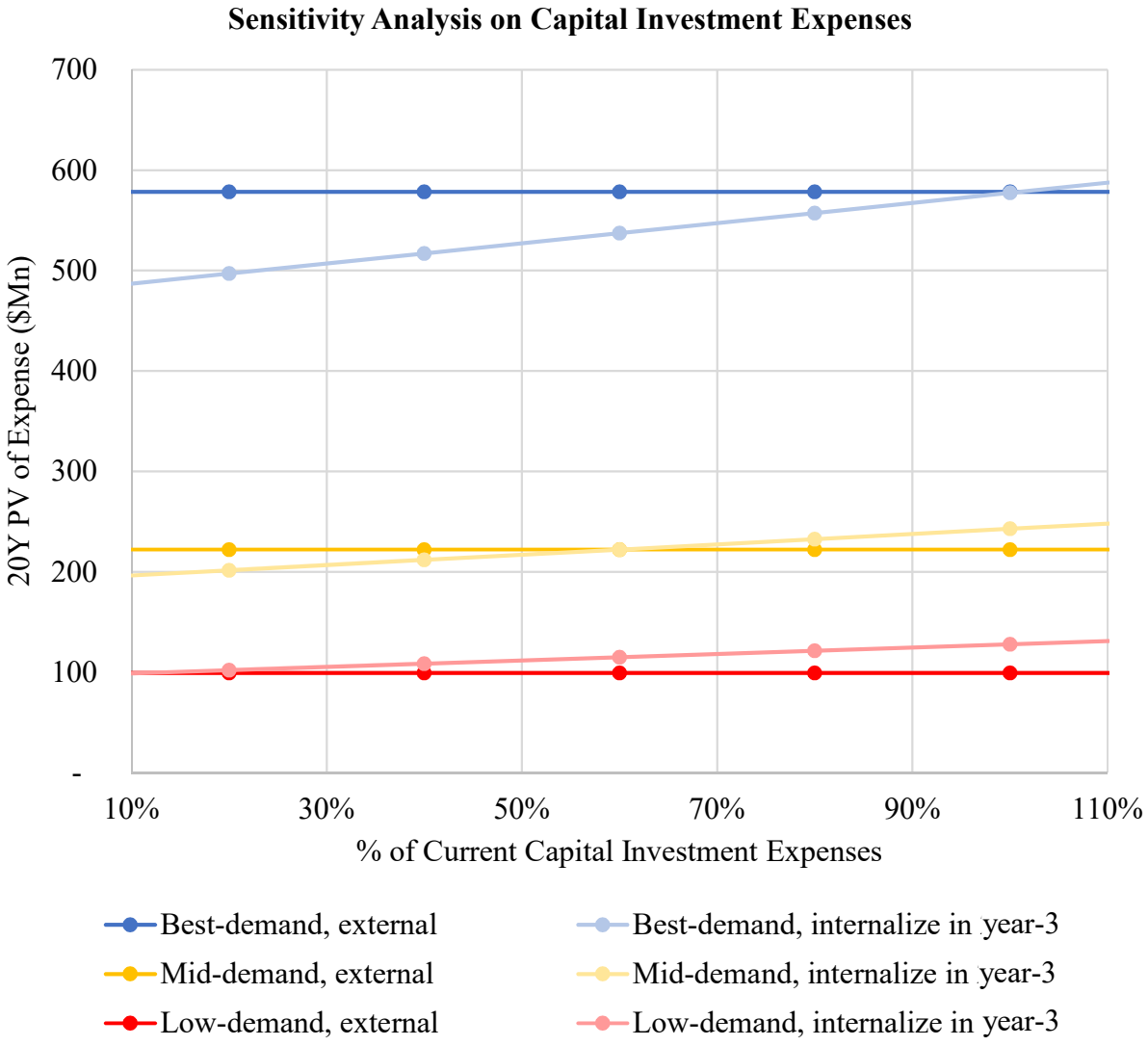

Figure 6-6. Sensitivity Analysis of Capital Investment Expense

Contract manufacturing organization (CMO) price

For the CMO price parameter, the results are a bit different than the other two. As can be seen in Figure 6-7, the internalization lines are flat, because changes in the CMO price will not affect the PV of expense when Amgen internalizes the production.

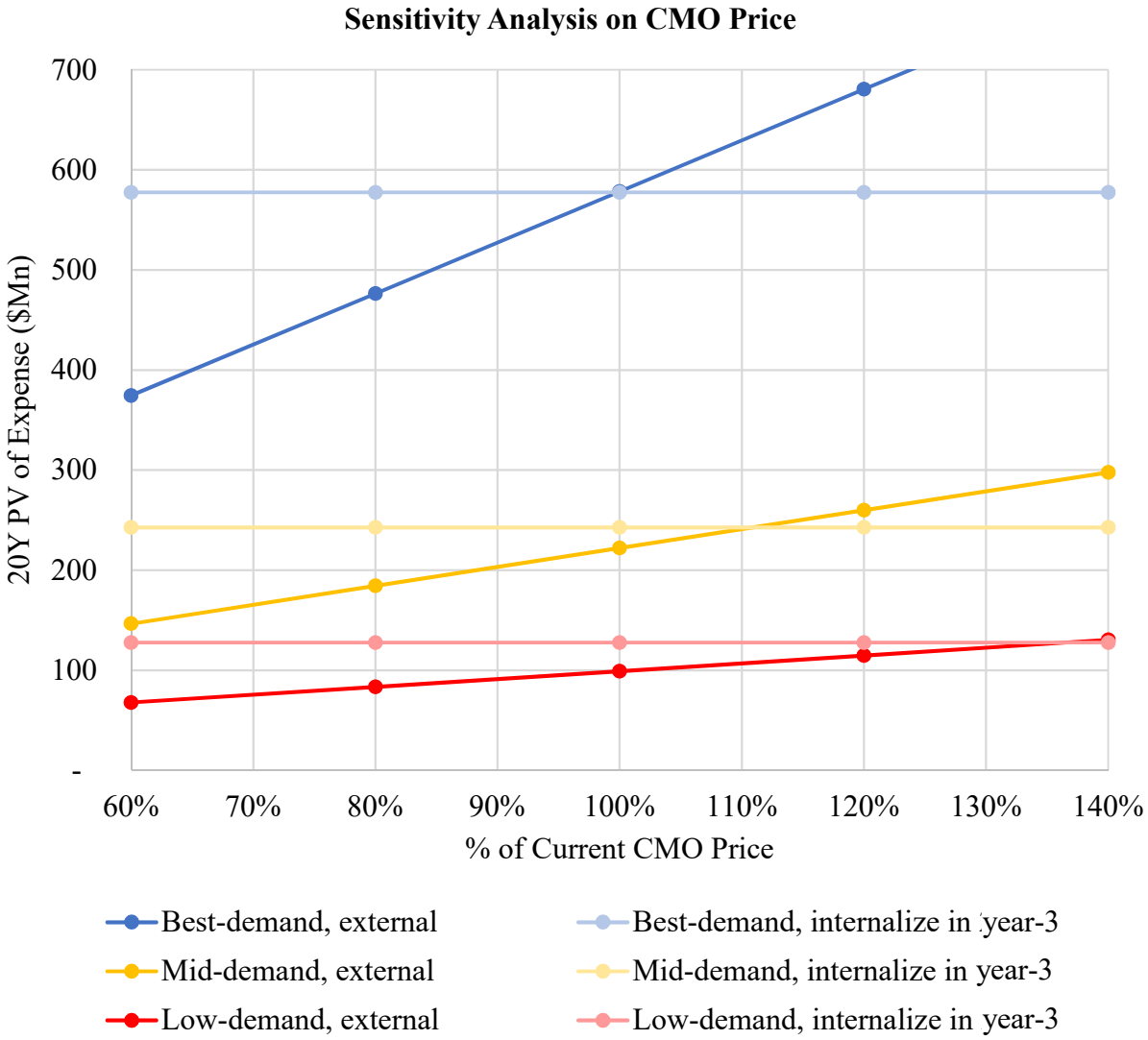

Figure 6-7. Sensitivity Analysis of CMO Price

Nevertheless, the impact of this parameter on the externalization scenario is rather strong. For example, under the mid-demand (low-demand) cases, if the CMO price is increased

to 13% (38%) higher than the current value, then internalizing becomes the better option, as it will be more expensive to pay the vendor compared to building Amgen's own facility.

The sensitivity analysis shows that the conclusion from the business model is quite sensitive to the values of the key input parameters. When the values of the key input parameters change, the resulting PV of Expense can vary a lot, to the extent that the better option can flip from externalization to internalization, and vice versa. Therefore, it is critical to obtain accurate and updated values for these key input parameters for the model to generate reliable results.

Chapter 7

Conclusions and Recommendations

Small Interfering RNA (siRNA) is a new class of therapeutics with the potential to treat diseases by inhibiting the expression of a gene. Amgen selected its first siRNA program, Asset #1, in 2017. Currently, Amgen has multiple siRNA programs in development, with the most mature, Asset #1, to launch to market in coming years.

Until recently, Amgen has been outsourcing the drug substance and drug product manufacturing to external manufacturers, but with a growing siRNA portfolio and the indication that siRNA effectiveness is promising, the building of a new facility is of great interest and value. This thesis helps Amgen shape its siRNA manufacturing strategy – whether Amgen should build a new facility to internalize its production or continue to outsource, and if the answer is the former, when should they start internalizing.

Based on the supply chain and business model developed in this thesis, it is recommended to **keep the siRNA DS and DP manufacturing external with the CMO and reassess around year-12/year-13** when Amgen has more accurate prediction about the potential siRNA asset demand level (high, medium, or low) to decide whether or not to internalize production.

In addition, it is suggested that Amgen should keep the model up to date by updating the input parameter values regularly and reassessing when new information becomes available, even before year-12/year-13 (the model inflection point). These regular

updates and reassessment are important because potential changes in the input parameter values can alter the recommendation of externalizing vs. internalizing, as presented in the sensitivity analysis in Chapter 6. Several key inputs that need to be regularly monitored and updated are demand profile (not only Asset #1, but also other siRNA programs in later years), DS CMO quotes, capital investment costs and its breakdown, and lastly, the amidites and DL prices.

Furthermore, Amgen needs to keep monitoring the market to understand the dynamics between supply and demand, the competitive landscape, and whether there are potential new DS suppliers or other CMOs. Finally, Amgen should rethink and innovate their siRNA process to further differentiate from its competitors. For example, Amgen can utilize new technology, implement continuous manufacturing, and consider potential cost-savings in the raw materials and solvents used in the production process.

Appendix A

Inputs for the Business Model

As discussed, there are two types of market for Asset #1: market A and market B. Market A will be tapped earlier, while market B will be penetrated quite later in the commercialization process. Based on the total target market share percentage, there are three demand level scenarios:

- **High-demand scenario** reaches 40% market for both market A (by year-15) and market B (by year-18)
- **Mid-demand scenario** reaches 40% market for market A (by year-15), and 10% for market B (by year-18)
- **Low-demand scenario** reaches 40% market for market A (by year-18)

Table A-1. Demand Projection with Three Level Cases

Demand projection summary												
	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Best case												
Total Patients	4,000	6,000	11,000	25,000	80,000	250,000	450,000	800,000	1,000,000	1,300,000	1,400,000	1,500,000
Total Net Sales (000s)	$800	$4,000	$15,000	$40,000	$150,000	$425,000	$900,000	$1,500,000	$2,000,000	$2,500,000	$2,650,000	$2,750,000
		2										
Mid-case												
Total Patients	4,000	6,000	11,000	25,000	50,000	100,000	200,000	300,000	350,046	400,000	430,000	450,000
Total Net Sales (000s)	$800	$4,000	$15,000	$40,000	$100,000	$200,000	$350,000	$500,000	$650,000	$750,000	$800,000	$850,000
Worst case												
Total Patients	4,000	6,000	11,000	25,000	45,000	70,000	90,000	100,000	105,000	107,000	108,000	109,000
Total Net Sales (000s)	$800	$4,000	$15,000	$40,000	$80,000	$125,000	$150,000	$175,000	$185,000	$190,000	$195,000	$197,500

Table A-2. Demand and Process Development FTE and OSE Inputs

Demand and Revenue Projections		year-0	year-1	year-2	year-3	year-4	year-5	year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
AMG 890																					
Clinical																					
Phase 3	kg	-	3.00	3.00	3.00	3.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Commercial																					
Total patients	# k	-	-	-	-	-	-	-	-	4.00	6.00	11.00	25.00	45.00	70.00	90.00	100.00	105.00	107.00	108.00	109.00
Volume sold	kg	-	-	-	-	-	-	-	-	0.30	3.60	6.60	15.00	27.00	42.00	54.00	60.00	63.00	64.20	64.80	65.40
Revenue	$ Mn	-	-	-	-	-	-	-	-	0.40	4.00	15.00	40.00	80.00	125.00	150.00	175.00	185.00	190.00	195.00	197.50
Others																					
PPQ	kg	-	-	-	-	-	-	14.00	-	-	-	-	-	-	-	-	-	-	-	-	-
people for clinical trial	kg	-	-	-	-	-	-	-	-	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80

Operational Expenses - PD Development FTE & OSE		year-0	year-1	year-2	year-3	year-4	year-5	year-6	year-7	year-8	year-9
PD FTE costs	$ Mn	0.06	0.70	1.86	1.63	0.81	0.67	0.89	0.60	0.65	1.11
DS	$ Mn	-	0.38	2.30	0.75	0.81	0.81	0.91	0.50	0.13	0.13
DP	$ Mn	0.08	0.28	0.40	0.39	0.12	0.10	0.44	0.49	0.28	0.10
FDP	$ Mn	-	-	0.01	1.08	0.30	0.01	0.01	0.01	0.46	1.75
AS	$ Mn	0.04	0.73	1.00	1.04	0.37	0.36	0.42	0.19	0.42	0.24
XPD	$ Mn	-	0.02	0.02	-	0.03	0.05	-	-	-	-
PD OSE costs	$ Mn	0.01	0.16	2.50	2.56	0.47	0.18	0.22	0.14	0.09	0.30
DS	$ Mn	-	0.12	0.24	0.24	0.26	0.26	0.29	0.16	0.04	0.04
DP	$ Mn	0.01	0.05	0.06	0.06	0.02	0.02	0.07	0.08	0.05	0.02
FDP	$ Mn	-	-	-	0.58	0.58	-	-	-	-	0.50
AS	$ Mn	0.01	0.16	0.22	0.23	0.08	0.08	0.09	0.04	0.09	0.05
XPD	$ Mn	-	-	4.48	4.01	0.01	-	-	-	-	-
Incremental to internalize	$ Mn	-	-	-	-	-	-	-	-	-	-
AS	$ Mn	-	-	-	-	-	-	0.68	0.98	0.57	0.04

The demand level is dynamic in the model, meaning that the user can choose which demand level they want to simulate for the analysis. Before commercialization, there is volume needed for clinical trial phase in year-1 to year-4, and development in year-6 to make sure Amgen is ready for commercialization production. Additionally, along the years even after commercialization, Amgen still needs to support the patients who participated in the clinical trial free of charge. It is assumed that Asset #1 will have predefined doses a year, with predefined mg of DS per vial needed. However, in year-8, as it is planned to launch in the middle of the year, there is only half of the predefined annual doses in that year. As presented in Table A-2, the process development expenses need an incremental cost to internalize on the AS group to build internal analytics capability.

Table A-3. COGS, Capital, and Other Inputs

Cost of Goods Sold				
Internal		**DS**	**DP**	**FDP**
Raw materials	$/kg		20,000	7,000
1 kg	$/kg	290,000		
10 kg	$/kg	285,000		
100 kg	$/kg	280,000		
Overheads costs	$/kg		115,000	
Overall average costs	$/kg		116,000	12,000
External				
CMO rate				
Clinical	$/kg	1,400,000	190,000	
Commercial	$/kg	658,000	40,000	
One-time development cost	$ Mn	700,000	200,000	

Other inputs		
Batch and Dosage		
1 lot (internal)	vials	
1 lot (external)	vials	
1 vial dosage	mg/vial	
Batch size (internal)	kg/batch	
Batch size (internal)	kg/batch	
# injections/yr/patient	vials/yr	
General		
Annual discount rate	%	8%
Depreciation timeline		
Non-building	years	10
Building	years	40

OSE % of FTE costs		
OSE CW	%	50%
FTE PD	$ Mn/yr	0.13
FTE CW	$ Mn/yr	0.13

Capacity progression																	
		1:1 scenario								1:3 scenario							
		24 x 5				24 x 7				24 x 5				24 x 7			
Maximum capacity	kg/yr	36	51	87	101	72	89	161	178	54	81	135	162	102	130	232	259
Capital investment cost	$ Mn	27.4	30.2	63.7	69.2	27.4	30.2	63.7	69.2	31.6	34.7	71.9	78.2	31.6	34.7	71.9	78.2
Respective CW FTE #	#	5	7	9	14	8	10	16	20	5	6	10	12	8	10	15	19
Respective CW FTE cost	$ Mn	0.6	0.9	1.1	1.8	1.0	1.3	2.0	2.5	0.6	0.8	1.3	1.5	0.9	1.2	1.9	2.4
OSE % of FTE CW	%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Respective CW OSE cost	$ Mn	0.3	0.4	0.6	0.9	0.5	0.6	1.0	1.3	0.3	0.4	0.6	0.8	0.5	0.6	0.9	1.2
Maximum FTE #	#	6	8	6	8	9	6	9	6	6	7	6	7	8	11	8	11
Minimum FTE #	#	2	4	2	4	4	5	4	5	3	4	3	4	4	5	4	5

Maximum equipment utilization	%	80%	Multiplier 24x5 to 24x7	1.4

Time to build (incl. ramp up & inspection)		
Building (1st time)	years	2.00
Equipment lead-time	years	1.00

Capital costs		
Building (1st time)	$ Mn	15.00

Please note that in Table A-3, the "batch and dosage" inputs are redacted to preserve the confidentiality for Amgen.

COGS are laid out in the Table A-3, modeled based on internal historical average data, and CMO quotations. For FDP and DP, the cost for internal commercialization cannot be broken down into granular cost items (raw materials, FTE, etc.), therefore a lumpsum internal cost per vial (called cost-per-unit, or CPU, at Amgen) is used. Raw materials and consumables are extracted from previous CMO reports who made the materials for Amgen before, to get the measurement and magnitude of each raw material and consumable for a specific yield of DS. For the raw materials making up to 80% of total cost, a quotation from another vendor is obtained to understand the price point in 2020.

For each of the facility setup with its respective annual capacity, in Table A-3, there are minimum and maximum required numbers of contract workers (CW, FTE for manufacturing), as there is some downtime in the manufacturing process along the year. In this case, a slightly higher than average to calculate the respective FTE costs for each facility setup is taken. OSE costs is assumed to be 50% of total FTE costs based on finance's historical data. In Table A-3 as well, the capital costs for building and non-building (equipment, software, etc.) are differentiated. Building capital costs for the first time – first suite – is 15Mn USD, and to build another suite the additional building capital cost is 60% of 15Mn USD, that is 9Mn USD. The capital costs in the bordered table is the non-building capital costs. The lead time for building is two years, and for non-building is one year. This means to get the facility set-up for the first time, it will need the total of three years, including commissioning, inspection, and quality checking, until it is completely ready to run.

Other inputs including annual discount rate of 8%, and depreciation of 10 years for non-building and 40 years of building. Additionally, some key assumptions in this model are:

- FTE and OSE costs (for internal) and CMO costs (for external) covers testing and QC expenses

- Equal distribution of capital within the lead time number of years
- No reusing of consumables (i.e. filters), assuming a linear increase with the volume produced, as there are no exact studies yet. This is a caveat for cost improvements
- For manufacturing FTE, a slightly above average number is used (compared to minimum and maximum requirements) to give buffer for not-yet-calculated support FTEs (i.e. solution/buffer preparation, moving things, etc.)
- Not yet including FTEs for engineering team and technology transfers
- Assume 48 weeks of operations in a year

Appendix B

Business Model Results

Below are the summaries of model result run on high-demand, mid-demand, and low-demand level cases. As discussed in the thesis, in mid-demand and low-demand cases, it will not make sense to internalize, as it is most optimized to always keep external. On the other hand, for high-demand level, it is optimal – least PV of Expense – if Amgen starts internalizing in year-13, which means start building the facility in year-10.

Even though it is the least PV of Expense, it is not recommended to start building the facility in year-10, as at that time, based on the demand projection in Table 6-1, Amgen has not tapped market B, thus it cannot be deduced yet whether the demand level will be high, medium, or low – posing Amgen to an enormous risk. As discussed in Chapter 6, it is recommended to reassess in year-12/13 when the demand trend is more mature.

Here, the models for high-level demand on all scenarios (definitions in Table 4-2), and Optimized Scenario (in this case, internalize in year-13) are presented. The reason why the high-level demand case is presented instead of the other demand levels is because it has clear differentiation between the three predefined scenarios and the most optimized one identified by the mixed integer model.

Table B-1. Summary of Model Result on High-demand Level

Summary						
		Scenario #1	Scenario #2	Scenario #3	Optimized	Demand scenario:
Clinical		External	External	Internal (year-3)	External	(●) High-demand
Commercial		External	Internal (year-6)	Internal	Internal (year-13)	( ) Mid-demand
Financials results						( ) Low-demand
20-year PV of Expense	$ Mn	578	569	576	557	
10-year PV of Expense	$ Mn	29	59	65	29	Calculate
Avg. revenue/kg	$ Mn/kg	3.2	3.2	3.2	3.2	
Avg. COGS/kg	$ Mn/kg	0.5	0.4	0.4	0.4	
DS avg. cost/gr	$/gr	474.1	301.4	299.7	301.7	
DP avg. cost/unit	$/unit	13.4	11.0	11.0	11.0	
FDP avg. cost/unit	$/unit	3.5	3.5	3.5	3.5	
Breakeven # years	# years	11.9	12.7	12.8	12.6	
COGS %	%	17%	14%	14%	14%	

Table B-2. Summary of Model Result on Mid-demand Level

Summary						
		Scenario #1	Scenario #2	Scenario #3	Optimized	Demand scenario:
Clinical		External	External	Internal (year-3)	External	( ) High-demand
Commercial		External	Internal (year-6)	Internal	External	(●) Mid-demand
Financials results						( ) Low-demand
20-year PV of Expense	$ Mn	222	236	243	222	
10-year PV of Expense	$ Mn	29	59	65	29	Calculate
Avg. revenue/kg	$ Mn/kg	3.1	3.1	3.1	3.1	
Avg. COGS/kg	$ Mn/kg	0.5	0.5	0.5	0.5	
DS avg. cost/gr	$/gr	482.0	317.1	312.2	477.3	
DP avg. cost/unit	$/unit	13.4	11.0	11.0	11.0	
FDP avg. cost/unit	$/unit	3.5	3.5	3.5	3.5	
Breakeven # years	# years	11.9	12.7	12.7	11.9	
COGS %	%	18%	15%	15%	18%	

Table B-3. Summary of Model Result on Low-demand Level

Summary						
		Scenario #1	Scenario #2	Scenario #3	Optimized	Demand scenario:
Clinical		External	External	Internal (year-3)	External	( ) High-demand
Commercial		External	Internal (year-6)	Internal	External	( ) Mid-demand
Financials results						(●) Low-demand
20-year PV of Expense	$ Mn	99	121	128	99	
10-year PV of Expense	$ Mn	29	59	65	29	Calculate
Avg. revenue/kg	$ Mn/kg	2.9	2.9	2.9	2.9	
Avg. COGS/kg	$ Mn/kg	0.6	0.5	0.5	0.6	
DS avg. cost/gr	$/gr	505.9	358.9	344.3	491.8	
DP avg. cost/unit	$/unit	13.4	11.0	11.0	11.0	
FDP avg. cost/unit	$/unit	3.5	3.5	3.5	3.5	
Breakeven # years	# years	11.9	12.9	12.9	11.9	
COGS %	%	20%	18%	18%	20%	

Table B-4. Business Model on Scenario 1, High-demand Level

Scenario #1																				
Financials projection																				
		year-0	year-1	year-2	year-3	year-4	year-5	year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Operations																					
Volume needed	kg	-	3.0	3.0	3.0	3.0	-	14.0	-	2.1	5.4	8.4	16.8	49.8	151.8	271.8	481.8	601.8	781.8	841.8	901.8
Clinical	kg	-	3.0	3.0	3.0	3.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Commercial	kg	-	-	-	-	-	-	-	-	0.3	3.6	6.6	15.0	48.0	150.0	270.0	480.0	600.0	780.0	840.0	900.0
Development	kg	-	-	-	-	-	-	14.0	-	-	-	-	-	-	-	-	-	-	-	-	-
people from clinical trials	kg	-	-	-	-	-	-	-	-	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Revenue	**$ Mn**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**0.4**	**4.0**	**15.0**	**40.0**	**150.0**	**425.0**	**900.0**	**1,500.0**	**2,000.0**	**2,500.0**	**2,650.0**	**2,750.0**
	$ Mn	-	-	-	-	-	-	-	-	0.4	4.0	15.0	40.0	150.0	425.0	900.0	1,500.0	2,000.0	2,500.0	2,650.0	2,750.0
Volume sold	kg	-	-	-	-	-	-	-	-	0.3	3.6	6.6	15.0	48.0	150.0	270.0	480.0	600.0	780.0	840.0	900.0
Cost of Goods Sold	**$ Mn**	**-**	**3.6**	**3.6**	**3.6**	**3.6**	**-**	**7.3**	**-**	**1.1**	**2.8**	**4.4**	**8.8**	**26.0**	**79.2**	**141.9**	**251.5**	**314.1**	**408.1**	**439.4**	**470.7**
CMO bills	$ Mn	-	3.6	3.6	3.6	3.6	-	7.1	-	1.1	2.8	4.3	8.6	25.4	77.4	138.6	245.7	306.9	398.7	429.3	459.9
Clinical	$ Mn	-	3.6	3.6	3.6	3.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DS	$ Mn	-	3.0	3.0	3.0	3.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DP	$ Mn	-	0.6	0.6	0.6	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Commercial	$ Mn	-	-	-	-	-	-	7.1	-	1.1	2.8	4.3	8.6	25.4	77.4	138.6	245.7	306.9	398.7	429.3	459.9
DS	$ Mn	-	-	-	-	-	-	6.6	-	1.0	2.5	3.9	7.9	23.4	71.3	127.7	226.4	282.8	367.4	395.6	423.8
DP	$ Mn	-	-	-	-	-	-	0.6	-	0.1	0.2	0.3	0.7	2.0	6.1	10.9	19.3	24.1	31.3	33.7	36.1
Lumpsum internal (detail N.A.)	$ Mn	-	0.0	0.0	0.0	0.0	-	0.2	-	0.0	0.1	0.1	0.2	0.6	1.8	3.3	5.8	7.2	9.4	10.1	10.8
FDP	$ Mn	-	0.0	0.0	0.0	0.0	-	0.2	-	0.0	0.1	0.1	0.2	0.6	1.8	3.3	5.8	7.2	9.4	10.1	10.8
Operating Expenses	**$ Mn**	**0.1**	**0.9**	**4.4**	**4.2**	**1.3**	**0.8**	**1.1**	**0.7**	**0.7**	**1.4**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
PD FTE Development	$ Mn	0.1	0.7	1.9	1.6	0.8	0.7	0.9	0.6	0.6	1.1	-	-	-	-	-	-	-	-	-	-
PD OSE Costs	$ Mn	0.0	0.2	2.5	2.6	0.5	0.2	0.2	0.1	0.1	0.3	-	-	-	-	-	-	-	-	-	-
Tech Transfers Cost	**$ Mn**	**-**	**0.2**	**-**	**-**	**-**	**-**	**-**	**0.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
One-time development cost	$ Mn	-	0.2	-	-	-	-	-	0.7	-	-	-	-	-	-	-	-	-	-	-	-
Operating Profit	**$ Mn**	**-**	**(3.6)**	**(3.6)**	**(3.6)**	**(3.6)**	**-**	**(7.3)**	**-**	**(0.7)**	**1.2**	**10.6**	**31.2**	**124.0**	**345.8**	**758.1**	**1,248.5**	**1,685.9**	**2,091.9**	**2,210.6**	**2,279.3**
CF	$ Mn	-	(3.6)	(3.6)	(3.6)	(3.6)	-	(7.3)	-	(0.7)	1.2	10.6	31.2	124.0	345.8	758.1	1,248.5	1,685.9	2,091.9	2,210.6	2,279.3
PV CF	$ Mn	-	(3.1)	(2.9)	(2.7)	(2.5)	-	(4.3)	-	(0.3)	0.5	4.6	12.4	45.6	117.7	239.0	364.4	455.6	523.5	512.2	489.0
Total Expenses	**$ Mn**	**0.1**	**4.7**	**8.0**	**7.8**	**4.9**	**0.8**	**8.4**	**1.4**	**1.8**	**4.2**	**4.4**	**8.8**	**26.0**	**79.2**	**141.9**	**251.5**	**314.1**	**408.1**	**439.4**	**470.7**
CF	$ Mn	0.1	4.7	8.0	7.8	4.9	0.8	8.4	1.4	1.8	4.2	4.4	8.8	26.0	79.2	141.9	251.5	314.1	408.1	439.4	470.7
PV CF	$ Mn	0.1	4.0	6.3	5.7	3.3	0.5	4.9	0.8	0.9	2.0	1.9	3.5	9.6	27.0	44.7	73.4	84.9	102.1	101.8	101.0
20-year PV of Expense	**$ Mn**	**578.4**																			

In Scenario 1, all the costs are CMO bills and internal cost for FDP – as there is no plan for externalization on FDP, thus in every scenario FDP is always internal. This Scenario is the most straightforward as there is no complexity in capacity progression and other internal costs. The 20-year PV of Expense is $578.4Mn USD.

Table B-5. Business Model on Scenario 2, High-demand Level

Scenario #2

Financials projection

		year-0	year-1	year-2	year-3	year-4	year-5	year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Operations (only for internal new sites)																					
Capacity progression details																					
Maximum capacity	kg	-	-	-	-	-	-	57.60	57.60	57.60	57.60	57.60	57.60	57.60	414.40	414.40	495.20	621.60	784.80	886.40	909.60
Checking suite numbers	Int.	-	-	-	-	-	-	1	1	1	1	1	1	1	1	1	2	2	2	3	3
[redacted]	Int.	-	-	-	-	-	-	1	1	1	1	1	1	1	-	-	-	-	-	1	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
[redacted]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	1	1	2	2
Checking capital	$ Mn	-	-	-	-	-	-	27.4	27.4	27.4	27.4	27.4	27.4	27.4	78.2	78.2	108.4	112.9	150.1	183.9	186.6
Checking capital Fin	$ Mn	-	-	-	-	-	-	27.4	-	-	-	-	-	-	50.8	-	30.2	4.5	37.2	33.8	2.7
Volume needed	kg	-	3.0	3.0	3.0	3.0	-	14.0	-	2.1	5.4	8.4	16.8	49.8	151.8	271.8	481.8	601.8	781.8	841.8	901.8
Clinical	kg	-	3.0	3.0	3.0	3.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Commercial	kg	-	-	-	-	-	-	-	-	0.3	3.6	6.6	15.0	48.0	150.0	270.0	480.0	600.0	780.0	840.0	900.0
Development	kg	-	-	-	-	-	-	14.0	-	-	-	-	-	-	-	-	-	-	-	-	-
people from clinical trials	kg	-	-	-	-	-	-	-	-	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
DS																					
Volume produced	kg	-	-	-	-	-	-	14.0	-	2.1	5.4	8.4	16.8	49.8	151.8	271.8	481.8	601.8	781.8	841.8	901.8
Average utilization	%	0%	0%	0%	0%	0%	0%	19%	0%	3%	8%	12%	23%	69%	29%	52%	78%	77%	80%	76%	79%
Revenue	**$ Mn**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**0.4**	**4.0**	**15.0**	**40.0**	**150.0**	**425.0**	**900.0**	**1,500.0**	**2,000.0**	**2,500.0**	**2,650.0**	**2,750.0**
	$ Mn	-	-	-	-	-	-	-	-	0.4	4.0	15.0	40.0	150.0	425.0	900.0	1,500.0	2,000.0	2,500.0	2,650.0	2,750.0
Volume sold	kg	-	-	-	-	-	-	-	-	0.3	3.6	6.6	15.0	48.0	150.0	270.0	480.0	600.0	780.0	840.0	900.0
Cost of Goods Sold	**$ Mn**	**-**	**3.6**	**3.6**	**3.6**	**3.6**	**-**	**7.2**	**1.4**	**2.3**	**3.7**	**4.9**	**8.3**	**22.0**	**67.9**	**116.8**	**204.7**	**254.4**	**329.6**	**356.7**	**382.0**
CMO bills	$ Mn	-	3.6	3.6	3.6	3.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DS	$ Mn	-	3.0	3.0	3.0	3.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DP	$ Mn	-	0.6	0.6	0.6	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CW FTE costs	$ Mn	-	-	-	-	-	-	0.6	0.6	0.6	0.6	0.6	0.6	0.6	2.4	2.4	3.3	3.6	4.3	5.3	5.6
DS	$ Mn	-	-	-	-	-	-	0.6	0.6	0.6	0.6	0.6	0.6	0.6	2.4	2.4	3.3	3.6	4.3	5.3	5.6
CW OSE costs	$ Mn	-	-	-	-	-	-	0.3	0.3	0.3	0.3	0.3	0.3	0.3	1.2	1.2	1.6	1.8	2.1	2.7	2.8
DS	$ Mn	-	-	-	-	-	-	0.3	0.3	0.3	0.3	0.3	0.3	0.3	1.2	1.2	1.6	1.8	2.1	2.7	2.8
Raw materials & consumables	$ Mn	-	-	-	-	-	-	4.0	-	0.6	1.6	2.4	4.8	14.2	42.5	76.1	134.9	168.5	218.9	235.7	252.5
DS	$ Mn	-	-	-	-	-	-	4.0	-	0.6	1.6	2.4	4.8	14.2	42.5	76.1	134.9	168.5	218.9	235.7	252.5
Overhead expenses	$ Mn	-	-	-	-	-	-	0.6	0.6	0.6	0.6	0.6	0.6	0.6	2.4	2.4	3.3	3.6	4.3	5.3	5.6
DS	$ Mn	-	-	-	-	-	-	0.6	0.6	0.6	0.6	0.6	0.6	0.6	2.4	2.4	3.3	3.6	4.3	5.3	5.6
Lumpsum internal (detail N.A.)	$ Mn	-	0.0	0.0	0.0	0.0	-	1.8	-	0.3	0.7	1.1	2.2	6.4	19.4	34.8	61.7	77.0	100.1	107.8	115.4
DP	$ Mn	-	-	-	-	-	-	1.6	-	0.2	0.6	1.0	1.9	5.8	17.6	31.5	55.9	69.8	90.7	97.6	104.6
FDP	$ Mn	-	0.0	0.0	0.0	0.0	-	0.2	-	0.0	0.1	0.1	0.2	0.6	1.8	3.3	5.8	7.2	9.4	10.1	10.8
Operating Expenses	**$ Mn**	**0.1**	**0.9**	**4.4**	**4.2**	**1.3**	**0.8**	**1.1**	**0.7**	**0.7**	**1.4**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
PD FTE Development	$ Mn	0.1	0.7	1.9	1.6	0.8	0.7	0.9	0.6	0.6	1.1	-	-	-	-	-	-	-	-	-	-
PD OSE Costs	$ Mn	0.0	0.2	2.5	2.6	0.5	0.2	0.2	0.1	0.1	0.3	-	-	-	-	-	-	-	-	-	-
Tech Transfers Cost	**$ Mn**	**-**	**0.2**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
One-time development cost	$ Mn	-	0.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

		year-0	year-1	year-2	year-3	year-4	year-5	year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Capital Expenditures	**$ Mn**	**-**	**-**	**-**	**7.5**	**34.9**	**-**	**-**	**-**	**-**	**-**	**-**	**41.7**	**16.6**	**37.7**	**33.5**	**22.0**	**34.9**	**2.7**	**-**	**-**
First-time	$ Mn	-	-	-	15.0	-	-	-	-	-	-	-	-	15.0	-	-	15.0	-	-	-	-
Additional	$ Mn	-	-	-	-	27.4	-	-	-	-	-	-	41.7	9.1	30.2	33.5	14.5	27.4	2.7	-	-
Total	$ Mn	-	-	-	15.0	27.4	-	-	-	-	-	-	41.7	24.1	30.2	33.5	29.5	27.4	2.7	-	-
Operating profit	**$ Mn**	**-**	**(3.6)**	**(3.6)**	**(3.6)**	**(3.6)**	**-**	**(7.2)**	**(1.4)**	**(1.9)**	**0.3**	**10.1**	**31.7**	**128.0**	**358.7**	**783.2**	**1,295.3**	**1,743.5**	**2,169.2**	**2,293.3**	**2,368.0**
Depreciation	$ Mn	-	-	-	-	-	-	-	3.1	3.1	3.1	3.1	3.1	3.1	3.1	7.3	8.2	11.6	12.2	13.6	16.8
Building	$ Mn	-	-	-	-	-	-	-	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.8	0.8	0.8	1.1
Building capital (done)	$ Mn	-	-	-	-	-	-	15.0	-	-	-	-	-	-	-	-	15.0	-	-	15.0	-
Non-building	$ Mn	-	-	-	-	-	-	-	2.7	2.7	2.7	2.7	2.7	2.7	2.7	6.9	7.8	10.8	11.4	12.9	15.6
Non-building capital (done)	$ Mn	-	-	-	-	-	-	27.4	-	-	-	-	-	-	41.7	9.1	30.2	33.5	14.5	27.4	2.7
CF	$ Mn	-	(3.6)	(3.6)	(11.1)	(38.6)	-	(7.2)	1.7	1.2	3.5	13.2	(6.9)	114.6	324.1	757.0	1,281.5	1,720.2	2,178.6	2,306.9	2,384.8
PV CF	$ Mn	-	(3.1)	(2.9)	(8.2)	(26.2)	-	(4.2)	0.9	0.6	1.6	5.7	(2.8)	42.1	110.4	238.6	374.0	464.9	545.2	534.5	511.6
Total Expenses	**$ Mn**	**0.1**	**4.7**	**8.0**	**15.3**	**39.8**	**0.8**	**8.3**	**2.1**	**3.0**	**5.1**	**4.9**	**50.1**	**38.5**	**104.0**	**150.3**	**226.7**	**291.4**	**333.6**	**356.7**	**382.0**
CF	$ Mn	0.1	4.7	8.0	15.3	39.8	0.8	8.3	2.1	3.0	5.1	4.9	50.1	38.5	104.0	150.3	226.7	291.4	333.6	356.7	382.0
PV CF	$ Mn	0.1	4.0	6.3	11.2	27.1	0.5	4.8	1.2	1.5	2.4	2.1	19.9	14.2	35.4	47.4	66.2	78.8	83.5	82.7	82.0
20-year PV of Expense	**$ Mn**	**569.4**																			

Here, the complexity comes into play, as there is internal capacity progression and costs in the model. As shown in the capacity progression part in the first section of the model (red boxes), the first facility setup in year-6 is the smallest setup – one suite, one TFF, 24x5 operations – for seven years, and then it increases gradually until in year-19 Amgen will need two TFFs in each of the five suites required, four of which need 24x7 operations and one 24x5. It can also be seen that at the beginning when the internal facility does not exist yet, there are CMO costs, whereas after the facility is done, it decreases to zero.

In this case, the 20-year PV of Expense is $569Mn USD, around $8Mn USD (or 2%) lower than Scenario 1.

Table B-6. Business Model on Scenario 3, High-demand Level

Scenario #3																					
Financials projection																					
		year-0	year-1	year-2	year-3	year-4	year-5	year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Operations (only for internal new sites)																					
Capacity progression details																					
Maximum capacity	kg	-	-	-	57.60	57.60	57.60	57.60	57.60	57.60	57.60	57.60	57.60	57.60	414.40	414.40	495.20	621.60	784.80	886.40	909.60
Checking suite numbers	Int.	-	-	-	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	3	3
[illegible]	Int.	-	-	-	1	1	1	1	1	1	1	1	1	1	-	-	-	-	-	1	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	1	1	2	2
Checking capital	$ Mn	-	-	-	27.4	27.4	27.4	27.4	27.4	27.4	27.4	27.4	27.4	27.4	78.2	78.2	108.4	112.9	150.1	183.9	186.6
Checking capital Fin	$ Mn	-	-	-	27.4	-	-	-	-	-	-	-	-	-	50.8	-	30.2	4.5	37.2	33.8	2.7
Volume needed	kg	-	3.0	3.0	3.0	3.0	-	14.0	-	2.1	5.4	8.4	16.8	49.8	151.8	271.8	481.8	601.8	781.8	841.8	901.8
Clinical	kg	-	3.0	3.0	3.0	3.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Commercial	kg	-	-	-	-	-	-	-	-	0.3	3.6	6.6	15.0	48.0	150.0	270.0	480.0	600.0	780.0	840.0	900.0
Development	kg	-	-	-	-	-	-	14.0	-	-	-	-	-	-	-	-	-	-	-	-	-
people from clinical trials	kg	-	-	-	-	-	-	-	-	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
DS																					
Volume produced	kg	-	3.0	3.0	3.0	3.0	-	14.0	-	2.1	5.4	8.4	16.8	49.8	151.8	271.8	481.8	601.8	781.8	841.8	901.8
Average utilization	%	0%	0%	0%	4%	4%	0%	19%	0%	3%	8%	12%	23%	69%	29%	52%	78%	77%	80%	76%	79%
Revenue	**$ Mn**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**0.4**	**4.0**	**15.0**	**40.0**	**150.0**	**425.0**	**900.0**	**1,500.0**	**2,000.0**	**2,500.0**	**2,650.0**	**2,750.0**
	$ Mn	-	-	-	-	-	-	-	-	0.4	4.0	15.0	40.0	150.0	425.0	900.0	1,500.0	2,000.0	2,500.0	2,650.0	2,750.0
Volume sold	kg	-	-	-	-	-	-	-	-	0.3	3.6	6.6	15.0	48.0	150.0	270.0	480.0	600.0	780.0	840.0	900.0
Cost of Goods Sold	**$ Mn**	**-**	**3.6**	**3.6**	**2.7**	**2.7**	**1.4**	**7.2**	**-**	**2.3**	**3.7**	**4.9**	**8.3**	**22.0**	**67.9**	**116.8**	**204.7**	**254.4**	**329.6**	**356.7**	**382.0**
CMO bills	$ Mn	-	3.6	3.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DS	$ Mn	-	3.0	3.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DP	$ Mn	-	0.6	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CW FTE costs	$ Mn	-	-	-	0.6	0.6	0.6	0.6	-	0.6	0.6	0.6	0.6	0.6	2.4	2.4	3.3	3.6	4.3	5.3	5.6
DS	$ Mn	-	-	-	0.6	0.6	0.6	0.6	-	0.6	0.6	0.6	0.6	0.6	2.4	2.4	3.3	3.6	4.3	5.3	5.6
CW OSE costs	$ Mn	-	-	-	0.3	0.3	0.3	0.3	-	0.3	0.3	0.3	0.3	0.3	1.2	1.2	1.6	1.8	2.1	2.7	2.8
DS	$ Mn	-	-	-	0.3	0.3	0.3	0.3	-	0.3	0.3	0.3	0.3	0.3	1.2	1.2	1.6	1.8	2.1	2.7	2.8
Raw materials & consumables	$ Mn	-	-	-	0.9	0.9	-	4.0	-	0.6	1.6	2.4	4.8	14.2	42.5	76.1	134.9	168.5	218.9	235.7	252.5
DS	$ Mn	-	-	-	0.9	0.9	-	4.0	-	0.6	1.6	2.4	4.8	14.2	42.5	76.1	134.9	168.5	218.9	235.7	252.5
DP	$ Mn	-	-	-	0.1	0.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Overhead expenses	$ Mn	-	-	-	0.9	0.9	0.6	0.6	-	0.6	0.6	0.6	0.6	0.6	2.4	2.4	3.3	3.6	4.3	5.3	5.6
DS	$ Mn	-	-	-	0.6	0.6	0.6	0.6	-	0.6	0.6	0.6	0.6	0.6	2.4	2.4	3.3	3.6	4.3	5.3	5.6
DP	$ Mn	-	-	-	0.3	0.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lumpsum internal (detail N.A.)	$ Mn	-	0.0	0.0	0.0	0.0	-	1.8	-	0.3	0.7	1.1	2.2	6.4	19.4	34.8	61.7	77.0	100.1	107.8	115.4
DP	$ Mn	-	-	-	-	-	-	1.6	-	0.2	0.6	1.0	1.9	5.8	17.6	31.5	55.9	69.8	90.7	97.6	104.6
FDP	$ Mn	-	0.0	0.0	0.0	0.0	-	0.2	-	0.0	0.1	0.1	0.2	0.6	1.8	3.3	5.8	7.2	9.4	10.1	10.8
Operating Expenses	**$ Mn**	**0.1**	**0.9**	**4.4**	**4.2**	**1.3**	**0.8**	**1.1**	**0.7**	**0.7**	**1.4**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
PD FTE Development	$ Mn	0.1	0.7	1.9	1.6	0.8	0.7	0.9	0.6	0.6	1.1	-	-	-	-	-	-	-	-	-	-
PD OSE Costs	$ Mn	0.0	0.2	2.5	2.6	0.5	0.2	0.2	0.1	0.1	0.3	-	-	-	-	-	-	-	-	-	-

		year-0	year-1	year-2	year-3	year-4	year-5	year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Capital Expenditures	**$ Mn**	**7.5**	**34.9**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**41.7**	**16.6**	**37.7**	**33.5**	**22.0**	**34.9**	**2.7**	**-**	**-**
First-time	$ Mn	15.0	-	-	-	-	-	-	-	-	-	-	-	15.0	-	-	15.0	-	-	-	-
Additional	$ Mn	-	27.4	-	-	-	-	-	-	-	-	-	41.7	9.1	30.2	33.5	14.5	27.4	2.7	-	-
Total	$ Mn	15.0	27.4	-	-	-	-	-	-	-	-	-	41.7	24.1	30.2	33.5	29.5	27.4	2.7	-	-
Operating profit	**$ Mn**	**-**	**(3.6)**	**(3.6)**	**(2.7)**	**(2.7)**	**(1.4)**	**(7.2)**	**-**	**(1.9)**	**0.3**	**10.1**	**31.7**	**128.0**	**358.7**	**783.2**	**1,295.3**	**1,743.5**	**2,169.2**	**2,293.3**	**2,368.0**
Depreciation	$ Mn	-	-	-	-	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	4.5	5.5	8.8	12.2	13.6	16.8
Building	$ Mn	-	-	-	-	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.8	0.8	0.8	1.1
Building capital (done)	$ Mn	-	-	-	15.0	-	-	-	-	-	-	-	-	-	-	-	15.0	-	-	15.0	-
Non-building	$ Mn	-	-	-	-	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	4.2	5.1	8.1	11.4	12.9	15.6
Non-building capital (done)	$ Mn	-	-	-	27.4	-	-	-	-	-	-	-	-	-	41.7	9.1	30.2	33.5	14.5	27.4	2.7
CF	$ Mn	(7.5)	(38.6)	(3.6)	(2.7)	0.4	1.7	(4.1)	3.1	1.2	3.5	13.2	(6.9)	114.6	324.1	754.2	1,278.7	1,717.4	2,178.6	2,306.9	2,384.8
PV CF	$ Mn	(6.9)	(33.1)	(2.9)	(2.0)	0.3	1.1	(2.4)	1.7	0.6	1.6	5.7	(2.8)	42.1	110.4	237.8	373.2	464.2	545.2	534.5	511.6
Total Expenses	**$ Mn**	**7.6**	**39.4**	**8.0**	**6.9**	**4.0**	**2.2**	**8.3**	**0.7**	**3.0**	**5.1**	**4.9**	**50.1**	**38.5**	**104.0**	**150.3**	**226.7**	**291.4**	**333.6**	**356.7**	**382.0**
CF	$ Mn	7.6	39.4	8.0	6.9	4.0	2.2	8.3	0.7	3.0	5.1	4.9	50.1	38.5	104.0	150.3	226.7	291.4	333.6	356.7	382.0
PV CF	$ Mn	7.0	33.8	6.3	5.1	2.7	1.4	4.8	0.4	1.5	2.4	2.1	19.9	14.2	35.4	47.4	66.2	78.8	83.5	82.7	82.0
20-year PV of Expense	**$ Mn**	**576.4**																			

The capacity progression in Scenario 3 does not differ that much from Scenario 2. In Scenario 3, the starting point of internalization is earlier, which is year-3, therefore it will start with the smallest setup – one suite, one TFF, 24x5 operations – earlier and will last 10 years (three years longer than Scenario 2, as the internalization in Scenario 3 starts three years earlier).

In this case, the 20-year PV of Expense is higher than Scenario 2, but lower than Scenario 1 – only 1% lower, or around $3Mn USD.

Table B-7. Business Model on Optimized Scenario, High-Level Demand

		year-0	year-1	year-2	year-3	year-4	year-5	year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Optimized Scenario																					
Financials projection																					
Operations (only for internal new sites)																					
Capacity progression details																					
Maximum capacity	kg	-	-	-	57.60	57.60	57.60	57.60	57.60	57.60	57.60	57.60	57.60	57.60	414.40	414.40	495.20	621.60	784.80	886.40	909.60
Checking suite numbers	Int.	-	-	-	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	3	3
[illegible]	Int.	-	-	-	1	1	1	1	1	1	1	1	1	1	-	-	-	-	-	1	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
[illegible]	Int.	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	1	1	2	2
Checking capital	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	78.2	78.2	108.4	112.9	150.1	183.9	186.6
Checking capital Fin	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	78.2	-	30.2	4.5	37.2	33.8	2.7
Volume needed	kg	-	3.0	3.0	3.0	3.0	-	14.0	-	2.1	5.4	8.4	16.8	49.8	151.8	271.8	481.8	601.8	781.8	841.8	901.8
Clinical	kg	-	3.0	3.0	3.0	3.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Commercial	kg	-	-	-	-	-	-	-	-	0.3	3.6	6.6	15.0	48.0	150.0	270.0	480.0	600.0	780.0	840.0	900.0
Development	kg	-	-	-	-	-	-	14.0	-	-	-	-	-	-	-	-	-	-	-	-	-
people from clinical trials	kg	-	-	-	-	-	-	-	-	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
DS																					
Volume produced	kg	-	3.0	3.0	3.0	3.0	-	14.0	-	2.1	5.4	8.4	16.8	49.8	151.8	271.8	481.8	601.8	781.8	841.8	901.8
Yes/No	Bin.	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	1	1	1	1
Volume internal	kg	-	-	-	-	-	-	-	-	-	-	-	-	-	151.8	271.8	481.8	601.8	781.8	841.8	901.8
Volume external	kg	-	3.0	3.0	3.0	3.0	-	14.0	-	2.1	5.4	8.4	16.8	49.8	-	-	-	-	-	-	-
Average utilization	%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	29%	52%	78%	77%	80%	76%	79%
Revenue	**$ Mn**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**0.4**	**4.0**	**15.0**	**40.0**	**150.0**	**425.0**	**900.0**	**1,500.0**	**2,000.0**	**2,500.0**	**2,650.0**	**2,750.0**
	$ Mn	-	-	-	-	-	-	-	-	0.4	4.0	15.0	40.0	150.0	425.0	900.0	1,500.0	2,000.0	2,500.0	2,650.0	2,750.0
Volume sold	kg	-	-	-	-	-	-	-	-	0.3	3.6	6.6	15.0	48.0	150.0	270.0	480.0	600.0	780.0	840.0	900.0
Cost of Goods Sold	**$ Mn**	**-**	**3.6**	**3.6**	**3.6**	**3.6**	**-**	**7.3**	**-**	**1.1**	**2.8**	**4.4**	**8.8**	**26.0**	**67.9**	**116.8**	**204.7**	**254.4**	**329.6**	**356.7**	**382.0**
CMO bills	$ Mn	-	3.6	3.6	3.6	3.6	-	7.1	-	1.1	2.8	4.3	8.6	25.4	-	-	-	-	-	-	-
DS	$ Mn	-	3.0	3.0	3.0	3.0	-	6.6	-	1.0	2.5	3.9	7.9	23.4	-	-	-	-	-	-	-
DP	$ Mn	-	0.6	0.6	0.6	0.6	-	0.6	-	0.1	0.2	0.3	0.7	2.0	-	-	-	-	-	-	-
CW FTE costs	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	2.4	2.4	3.3	3.6	4.3	5.3	5.6
DS	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	2.4	2.4	3.3	3.6	4.3	5.3	5.6
CW OSE costs	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	1.2	1.2	1.6	1.8	2.1	2.7	2.8
DS	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	1.2	1.2	1.6	1.8	2.1	2.7	2.8
Raw materials & consumables	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	42.5	76.1	134.9	168.5	218.9	235.7	252.5
DS	$ Mn	-			-	-	-	-	-	-	-	-	-	-	42.5	76.1	134.9	168.5	218.9	235.7	252.5
DP	$ Mn	-			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Overhead expenses	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	2.4	2.4	3.3	3.6	4.3	5.3	5.6
DS	$ Mn	-			-	-	-	-	-	-	-	-	-	-	2.4	2.4	3.3	3.6	4.3	5.3	5.6
DP	$ Mn	-			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lumpsum internal (detail N.A.)	$ Mn	-	0.0	0.0	0.0	0.0	-	0.2	-	0.0	0.1	0.1	0.2	0.6	19.4	34.8	61.7	77.0	100.1	107.8	115.4
DP	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	17.6	31.5	55.9	69.8	90.7	97.6	104.6
FDP	$ Mn	-	0.0	0.0	0.0	0.0	-	0.2	-	0.0	0.1	0.1	0.2	0.6	1.8	3.3	5.8	7.2	9.4	10.1	10.8
Operating Expenses	**$ Mn**	**0.1**	**0.9**	**4.4**	**4.2**	**1.3**	**0.8**	**1.1**	**0.7**	**0.7**	**1.4**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
PD FTE Development	$ Mn	0.1	0.7	1.9	1.6	0.8	0.7	0.9	0.6	0.6	1.1	-	-	-	-	-	-	-	-	-	-
PD OSE Costs	$ Mn	0.0	0.2	2.5	2.6	0.5	0.2	0.2	0.1	0.1	0.3	-	-	-	-	-	-	-	-	-	-

		year-0	year-1	year-2	year-3	year-4	year-5	year-6	year-7	year-8	year-9	year-10	year-11	year-12	year-13	year-14	year-15	year-16	year-17	year-18	year-19
Tech Transfers Cost	**$ Mn**	**-**	**0.2**	**-**	**-**	**-**	**-**	**-**	**0.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
One-time development cost	$ Mn	-	0.2	-	-	-	-	-	0.7	-	-	-	-	-	-	-	-	-	-	-	-
Capital Expenditures	**$ Mn**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**7.5**	**67.7**	**16.6**	**37.7**	**33.5**	**22.0**	**34.9**	**2.7**	**-**	**-**
First-time	$ Mn	-	-	-	-	-	-	-	-	-	-	15.0	-	15.0	-	-	15.0	-	-	-	-
Additional	$ Mn	-	-	-	-	-	-	-	-	-	-	-	60.2	9.1	30.2	33.5	14.5	27.4	2.7	-	-
Total	$ Mn	-	-	-	-	-	-	-	-	-	-	15.0	60.2	24.1	30.2	33.5	29.5	27.4	2.7	-	-
Operating profit	**$ Mn**	**-**	**(3.6)**	**(3.6)**	**(3.6)**	**(3.6)**	**-**	**(7.3)**	**-**	**(0.7)**	**1.2**	**10.6**	**31.2**	**124.0**	**358.7**	**783.2**	**1,295.3**	**1,743.5**	**2,169.2**	**2,293.3**	**2,368.0**
Depreciation	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6.4	7.3	10.7	14.0	15.5	18.6
Building	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.4	0.4	0.8	0.8	0.8	1.1
Building capital (done)	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	15.0	-	15.0	-	-	15.0	-
Non-building	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6.0	6.9	9.9	13.3	14.7	17.5
Non-building capital (done)	$ Mn	-	-	-	-	-	-	-	-	-	-	-	-	-	60.2	9.1	30.2	33.5	14.5	27.4	2.7
CF	$ Mn	-	(3.6)	(3.6)	(3.6)	(3.6)	-	(7.3)	-	(0.7)	1.2	3.1	(36.4)	107.4	321.0	756.1	1,280.6	1,719.3	2,180.4	2,308.8	2,386.6
PV CF	$ Mn	-	(3.1)	(2.9)	(2.7)	(2.5)	-	(4.3)	-	(0.3)	0.5	1.3	(14.5)	39.5	109.3	238.3	373.8	464.7	545.7	535.0	512.0
Total Expenses	**$ Mn**	**0.1**	**4.7**	**8.0**	**7.8**	**4.9**	**0.8**	**8.4**	**1.4**	**1.8**	**4.2**	**11.9**	**76.4**	**42.6**	**104.0**	**150.3**	**226.7**	**291.4**	**333.6**	**356.7**	**382.0**
CF	$ Mn	0.1	4.7	8.0	7.8	4.9	0.8	8.4	1.4	1.8	4.2	11.9	76.4	42.6	104.0	150.3	226.7	291.4	333.6	356.7	382.0
PV CF	$ Mn	0.1	4.0	6.3	5.7	3.3	0.5	4.9	0.8	0.9	2.0	5.1	30.3	15.6	35.4	47.4	66.2	78.8	83.5	82.7	82.0
20-year PV of Expense	**$ Mn**	**556.5**																			

In the Optimized Scenario model, the results Scenario 3 is taken to look at the earliest possible internalization with the most optimized capacity progression, and then another mixed integer model is run to look at which year to start internalizing that will yield the least PV of Expense. A new binomial variable (red box) is introduced, the value of which will indicate internalize or externalize. One means internalize, and zero means externalize. In Table B-7 above, it is the most optimized to start internalization in the year of year-13, yielding a 20-year PV of Expense of $557Mn USD, or 4% lower than Scenario 1. This is by far the least PV of Expense found.

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