Capital Project Development in Biotechnology Industry

By
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B.Sc. in Mechanical and Industrial Engineering, University of Iceland, 2002

Submitted to the MIT Sloan School of Management and the Department of Civil and Environmental Engineering in Partial Fulfillment of the Requirements for the Degrees of

Master of Business Administration
AND
Master of Science in Civil and Environmental Engineering

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ABSTRACT

The biotechnology industry has experienced fast growth during the first 30 years of its existence but is now reaching a stage of maturity. Companies are being challenged by weak pipelines and patent expirations, as well as increasing regulation. Mergers and acquisitions are frequent, and companies are forced to reduce planned capital expenditures, as well as restructure with personnel cuts and facility reductions. This thesis focuses on the affect those changes are having on the development of capital projects. It researches the environment as it used to be and what is now bringing the changes. Through literature search and case study, the thesis aims to capture the reasons for why the main driver of new facilities construction has shifted from time to cost and the affect that is having on the management and delivery of such projects.

Thesis Supervisor: Donald Rosenfield
Title: Director, Leaders For Manufacturing Fellows Program

Thesis Supervisor: Fred Moavenzadeh
Title: James Mason Crafts Professor of Civil and Environmental Engineering and Engineering Systems
Director, Technology and Development Program
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I would like to take the opportunity to thank my family who gave me strength when I needed it the most and whose belief in me gave me the power to reach my goals. I would also like to thank my class for this wonderful two-year journey, especially all the LFM’08s. We reached this goal together.
Note on Proprietary Information

In order to protect proprietary Amgen information, the data presented throughout this thesis has been altered and does not represent the actual values used by Amgen, Inc. The dollar values have been disguised and names have been altered in order to protect competitive information where necessary.
Biographical Note

Asbjorg Kristinsdottir was born in Reykjavik, Iceland, where she graduated from the University of Iceland in 2002, with BSc degree in Mechanical- and Industrial Engineering. As a part of the undergraduate internships, Asbjorg worked on various projects for companies in different industries, such as Bakkavor Group, deCODE Genetics, and Century Aluminum. After graduating she worked for four years for the National Power Company in Iceland in the Engineering and Construction Division, on both geothermal and hydropower projects, including working on the project management team for the 690 MW Karahnjukar Hydroelectric Project.
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1 PART I: Introduction and Background

1.1 Introduction

This thesis is developed from a six-month internship at Amgen, a leading human therapeutics company in the biotechnology industry. The internship was focused on the construction of a new facility in one of their manufacturing locations.

The focus of the internship was intended to be on the cost estimates for the construction of the facility. However, during those six months, the company was faced with the same challenges as other companies in the industry. The nature of new project development was changing. The companies no longer had the capital to spend on new projects and had to cut back in expenditure, resulting in layoffs, facilities reductions, and overall changes to future project planning. The companies were forced to reassess the need for new capital projects, and thoroughly examine current project expenditures.

The new facility project at Amgen was planned as a major expansion to this manufacturing plant. It was intended to include formulation and fill, in a separate building with its own utilities as well as administrative building. As the internship started, the project had been going through the basis of design for over a year. The kick-off meeting had been held and the team was ready to move to the detailed design when Amgen announced that the need for the project had to be reassessed due to the challenges the company was being faced with as a result of the changes in the biotechnology industry. What initially was meant as a risk mitigation project with optimally designed facility with potential expansion capability as fitting to the overall site master plan had changed to simply building a facility that would be sufficient for the Food and Drug Administration (FDA) compliance. The desired strategy was no longer to go ahead with the optimal design, but to redesign to cut down cost as much as possible.

For the next six months the team worked on redesigning the facility. Several design alternatives were considered, ranging from the original design of a state of the art facility, to trying to fit the project scope into an already constructed shell at the plant. As the
design kept on changing, and the start date of construction was pushed back further, the focus of the internship shifted towards looking at the main drivers in a new capital project when the company is being faced with the urgency of having to construct a new facility, but not having capital to go ahead with the optimal design. What different construction management methods are desirable when a company in the biotechnology industry lacks capital and time, but still has the need to go ahead with the construction project? What gets sacrificed in terms of the cost, time, and quality of the project depending on the choice of approach?

In order to answer this question there is initially a need to take a close look into the biotechnology industry in the United States, to see where it is coming from and what is driving the changes today. After an industry analysis, the thesis discusses the construction of a new facility for a biotechnology company and follows up with a case study of the new facility construction at Amgen.

1.2 Biotechnology industry

The biotechnology industry originated in the 1970s, based largely on a recombinant DNA technique that was published by, Stanley Cohen of Stanford University and Herbert Boyer of the University of California (BioWorld, 2007). The recombinant DNA technique is a method of making proteins in cultured cells under controlled manufacturing conditions. In the biotechnology industry this biochemical science is used to produce on large scale products for human health, food supplies, and the environment.

1.2.1 Current market

Thirty years ago, the biotechnology companies were often founded by idealistic scientists and run more on vision than corporate experience. By the end of 2005 there were 1,415 biotechnology companies in the United States, of which 329 were publicly held (BioWorld, 2007). The industry has been growing fast, but despite there being enough of statistical evidence that highlight the growth across the healthcare research pipeline the industry is now showing signs of reaching maturity in its lifecycle. Evident are the strengthening pipelines, revenue growth, and progress towards profitability. This success
comes with challenges that are born from the convergence in time of innovative new products, newly profitable companies, and greater responsibility including escalating regulatory challenges and heightened investor scrutiny (Ernst & Young, 2007).

**Figure 1** State of growth of the biotechnology industry

The biotechnology products treat a wide range of health issues. With the aging population in the United States, the demand for the biotechnology medications remains strong. The established products, along with innovative new drug launches, are predicted to continue generating strong revenue for the companies. The pattern of strong growth can clearly be seen by looking at the performance of the publicly traded companies, based on the data from the financial statements (see example in Table 1). In the past few years, stock performance has been supported by major biotech acquisitions. The acquisition activity is generally high in the biotechnology industry due to the need to fill product pipeline gaps, acquire manufacturing capabilities, or to scale existing business segments.

---

1 Source: Adapted from a diagram used in a case prepared at the Keck Graduate Institute of Applied Life Sciences (Agrawal, Kelly, & Finegold, 2001)
According to Standard & Poor’s, the leading companies in the biotechnology industry are predicted to grow their market-weighted earnings per share (EPS) by about 20% from 2007 to 2009, based on solid revenue growth, increasing operating leverage, and the use of share buybacks (Standard & Poor's, 2008).

<table>
<thead>
<tr>
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<tbody>
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<td>Sales</td>
<td>32.1</td>
<td>28.1</td>
<td>28.4</td>
<td>24.3</td>
<td>21.4</td>
<td>19.3</td>
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<tr>
<td>Revenues</td>
<td>50.7</td>
<td>43.8</td>
<td>39.2</td>
<td>29.6</td>
<td>29.6</td>
<td>26.7</td>
</tr>
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<td>19.8</td>
<td>19.6</td>
<td>17.9</td>
<td>20.5</td>
<td>15.7</td>
<td>14.2</td>
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<td>5.4</td>
<td>9.4</td>
<td>4.6</td>
<td>5.6</td>
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<td>No. of Public Companies</td>
<td>329</td>
<td>331</td>
<td>314</td>
<td>318</td>
<td>342</td>
<td>339</td>
</tr>
<tr>
<td>No. of Companies</td>
<td>1,415</td>
<td>1,346</td>
<td>1,473</td>
<td>1,466</td>
<td>1,457</td>
<td>1,379</td>
</tr>
</tbody>
</table>

Table 1  US biotechnology industry statistics from 2000 to 2005

For the past few years the biotechnology industry has seen major changes. Most noticeable have been the increased regulatory constraints and challenges. This increased scrutiny has lead to rising sales and marketing expenditures as the companies have tried to replenish from the suffering of tarnished reputation.

The total market capitalization of the public biotechnology companies in 2007 was $338B (Yahoo! Finance, 2007). Over 50% of the market share is held by the top three biochemical companies, Amgen, Genentech, and Gilead Sciences. Although the industry has seen changes, the companies still bear the values of the entrepreneurial founders, who were driven by the desire to improve human lives rather than by aspirations of financial gain.

---

2 Source: Ernst & Young (BioWorld, 2007)
1.2.2 Amgen Inc.

Amgen is a leading human therapeutics company in the biotechnology industry. It was founded in 1980 and is headquartered in Southern California. The company engages in the discovery, development, manufacture, and marketing of health care products, for supportive cancer care, nephrology, inflammation, and oncology. It is a pioneer in the development of novel products and launched the biotechnology industry’s first blockbuster medicine. Today, the principal products include Akranesp and EPOGEN that stimulate the production of red blood cells to treat anemia; Neulasta and NEUPOGEN, which selectively stimulate the production of neutrophils, a type of white blood cell that helps the body fight infections; and ENBREL that blocks the biologic activity of tumor necrosis factor by inhibiting TNF, a substance induced in response to inflammatory and immunological responses, such as rheumatoid arthritis and psoriasis (Yahoo! Finance, 2008).

Amgen has six manufacturing locations in the United States and offices in more than 30 countries, with around twenty thousand employees. The company markets its products to healthcare providers including physicians or their clinics, dialysis centers, hospitals, and pharmacies primarily in the United States, Europe, and Canada.

Figure 2 Amgen’s operation worldwide

Source: Amgen Inc.
In 2006, Amgen had plans to engage in the largest manufacturing capacity expansion in the history of the biotechnology industry. The largest new capital projects were twofold. A major production site was planned in County Cork, Ireland. Once operational, this site would include capacity for process development, bulk protein production, formulation, fill and finish, as well as quality testing. This plant was meant to play a crucial role in the expansion of Amgen’s global manufacturing network, producing medicines to serve a growing number of patients in Europe and other parts of the world. Another major expansion was planned for the plant in Juncos, Puerto Rico, by constructing a new facility to manufacture EPOGEN and Akranesp. The company also planned to add a new formulation, fill and finish facility and additional bulk protein manufacturing capacity to the plant.

But the year of 2006 was difficult for Amgen despite strong growth of the biotechnology industry. The company recorded a 14.8% increase in sales, to $14.27 billion. On the other hand, net income was $2.95 billion, 19.7% less than in 2005, and earnings per share were $2.48, 15.4% less than the previous year (Truelove, 2007). Between the first and third quarters of 2007, sales of Akranesp, the company’s top product, slumped by 30% as after FDA changed the label in response to unconfirmed safety issues which restricted prescribing freedom of doctors. The company saw its stock sink, fueled partly by some analysts who questioned the company’s growth potential. With revenues driving the expenses, Amgen announced in August that year its plans to cut and restructure. The restructuring included reducing headcount by 12% to 14% of total staff, or 2,200 to 2,600 employees. To improve cash flow, the company set to reduce planned capital expenditures by about $1.9 billion during the 2007 to 2008 period. In addition, the company planned to close certain production operations and rationalize other facilities. With main focus on future growth, the company’s focus shifted from expansion towards building the framework around the highest priorities in research and development and operations. Executives at Amgen believed that restructuring would be completed by 2008 and would yield pre-tax savings of between $1 billion and $1.3 billion in 2008.
Following Amgen's global review on their business plans, they decided to reschedule the execution of its project to build a new manufacturing capacity in Ireland. No changes were planned for the amount of additional capacity intended to be developed in Ireland, the overall capital investment, and the number of staff it planned to employ, but the timeline was to be extended to allow for a more efficient and sequenced project execution (Amgen, 2007). However, the plan was to continue pursuing the project in their plant in Juncos, Puerto Rico.

1.2.3 Future outlook for the industry

The operating environment for the biotechnology industry is expected to continue facing the same challenges as emerged in 2007. With the government and the public keeping a close eye on the safety and cost of the products, the companies have already moved to a strategy of cost containment with various restructuring activities, lower capital spending, and focus on product development. The demand is expected to stay strong due to the aging population in the United States, with pricing pressure being the largest offset to the strong demand growth in driving revenue growth. However, FDA has become more conservative, which could contribute to a slowing industry pipeline.

According to Fitch Ratings, with lower capital spending the cash flow generation is predicted to remain stable and although shareholder-friendly activities will continue, it will be at a lesser extent due to decreased leverage buyout pressure associated with a tightening credit environment. Moreover, Fitch Ratings believes that acquisition activity will continue but that debt will remain relatively stable (Business Wire, 2007).

Merger and acquisition activity is expected to be the key driver of performance for the biotechnology industry, as companies seek to bolster slowing pipelines with products and technologies. In addition, several companies have announced aggressive share repurchase programs, leveraging their sizable operation cash flows (Standard & Poor's, 2008).
1.3 Summary

The companies in the biotechnology industry are moving from the glory days of fast growth where they had sufficient capability to finance new capital projects. The companies didn’t use to question the expenditure needed to complete the projects as fast as possible to meet the market demand. When building new facilities, the delivery of the project was primarily focused on the time. As it was often vital for the companies to move fast, they were willing to put up with high cost for the benefit of having the capacity needed. As times have changed, the companies have had to reassess the way they manage new capital projects. The companies need to choose to manage their projects in the most cost efficient way while they’re still under the pressure of moving fast due to the business drivers.

The following chapters of the thesis will look into the construction of new facilities in the biotechnology industry. They will assess the methods used to manage the construction, as well as the costs and benefits of choosing between those methods. As a case study of managing such a project in the new environment of the biotechnology industry, the thesis discusses the project arrangement and challenges faced for a construction of a new Amgen facility.
2 PART II: Pharmaceutical facilities

In the biotechnology industry, the companies incur high fixed cost to develop a drug, such as research and development (R&D) and investments in production facilities, but have relatively low marginal cost for manufacturing the drug. As the companies are likely to earn more on each additional unit of drug sold than they pay for producing that unit, it is most important to keep a low fixed cost. With limited resources, and as large-scale manufacturing continues to intensify, it is important for the companies to effectively strategize their new capital project development.

2.1 Project Life Cycle

To build and validate a new facility in accordance with the regulation guidance requires long lead times and heavy fixed costs. According to industry estimates, a new large-scale Active Pharmaceutical Ingredients (API) facility with a total bioreactor capacity of roughly 100,000 liters can take three to five years to build, and can cost from $200 to $400 million (Agrawal, Kelly, & Finegold, 2001). From the perspective of the owner, the project life cycle for a constructed facility may be illustrated schematically in Figure 3.

![Figure 3 Project life cycle of a constructed facility](image)

The stages of development do not have to be sequential. Some of them may require iteration and others can be carried out in parallel or with overlapping time frames, depending on nature, size and urgency of the project. It also depends on the in-house

---

4 Source: Schematically drawn project life cycle according to Project Management for Construction (Hendrickson, 2003) adapted for the process of capital project flow for Amgen Inc.
capabilities of the owner where there is need to seek professional services for the work. Due to the specialized nature of the biotechnology industry, the owners usually choose to develop the in-house knowledge to be deeply involved in the development of the project, and pick a team of designers and builders with whom they can develop good working relations over the years.

2.1.1 Business Case

The initiation of the new construction projects depends on several market drivers and resistors. Some examples include new product introduction, regulatory requirements, existing product capacity shortfalls, and process improvements (Mongiardo & Bobrow, 2005). Due to the amount of planning needed, the capital intensity and construction time, the most important factor in the business case is the long range demand forecasting.

For production capacity building strategies, companies in the biotechnology industry have cycled between having too little capacity to having too much capacity and have historically had extremely high capacity utilization rates. With large number of products in the pipeline the companies drive to build capacity, but as products fail clinical trials and with a downturn in the economy, the companies seek balance in their production capacity. In 1998 ENBREL, a drug that blocks the biologic activity of tumor necrosis, was first released for commercial use. After two years on the market it was so popular that the producer\(^5\) was unable to manufacture enough to meet demand and had to introduce a waiting list for prospective patients. This motivated both drug developers and contract manufacturing organizations (CMO’s) to invest in additional manufacturing capacity. From 2003 to 2006 the capacity for mammalian cell culture production\(^6\) increased by almost 200% (Business Insights, 2007). Despite this substantial expansion in manufacturing capacity there are concerns that the unequal distribution of it may lead

\(^5\) ENBREL was developed by researchers at the biotechnology company Immunex, which was subsequently acquired by Amgen in 2002.

\(^6\) Biotechnology drug manufacturing is primarily of two types: microbial manufacturing (products made from bacteria) and mammalian cell manufacturing (products made from complex mammalian cells).
to supply shortages, as majority of the capacity is being concentrated within fewer than 10 companies.

According to Business Insights the number of biotechnology products is expected to increase by about 50% to the year of 2010, and a closer look at the current research and development pipeline shows that the number of drugs in various stages of development, as well as the increasing demand for biotechnology products, will continue to grow the need for greater manufacturing capacity (Tulsi, 2006). For the capacity strategies it is becoming important for the companies to decide whether to internalize the production or outsource to CMO’s. Regulatory constraints in the biotechnology industry, as well as the immaturity of the technology, used to stand in the way of the companies exploring those options. However, now that the CMO’s have developed deeper understanding in the process, the risk of outsourcing the manufacturing has been reduced, making it a viable option for the companies to consider. What ultimately determines the decision is the cost relative to benefits.

The main advantages of outsourcing are lower capital investments and the associated reduction in investment risk. The biotechnology companies can thereby focus on the research and development and marketing of their products. In addition, for companies without manufacturing experience the outsourcing helps them avoid the steep learning curve. The disadvantages associated with outsourcing to a CMO include the challenges with finding a CMO that has the right fit of capacity and technology and relying on a 3rd party to be compliant to all regulatory bodies. The potential higher cost of the goods also decreases the company’s profit margin for the product (Beckman & Rosenfield, 2008). In addition, the pricing pressures drive the companies to seek for low cost by offshoring to countries that offer lower salaries, highly educated workers, and supportive governments. However, the cost savings alone are not sufficient measurement for the optimal facilities development strategy. Hidden costs and risks need to be carefully evaluated, such as maintaining control over the process, the intellectual property, and quality.

---

7 In many industries, outsourcing is done to obtain lower costs, but in the biotechnology industry this is not always the case.
The advantages of not outsourcing but rather building up the company’s own manufacturing capacity include the ability to design and build to optimize the process and build up in-house expertise, which is valuable for the company’s long term strategy and improvements for future products. It enables the company to maintain lower cost of goods and to have full control over quality and regulatory issues. The disadvantages include the risk involved in timing the capacity expansion, since decision needs to be made long before capacity needs are finalized. In addition, the capital investment is high and the fast improvements in new technologies may create obsolete or idle capacity.

The manufacturing strategy needs to be in place early, typically prior to Phase III, in order to make registration batches and produce market launch material from same facility. However, there are many uncertainties with making an early decision, with challenges in failures from clinical to approval, regulatory, and commercial. The timing of capacity expansion is critical, or as stated in the report In Vivo in December 2001: “You have to have the internal fortitude to invest in unique manufacturing sites. And if you want to be in biologics big time, it’s too late to start thinking about manufacturing once your molecules are in development. It takes a little bit of foresight and sometimes sticking your neck on the line” (Welch, 2003).

![Timeline for antibody project compared to timeline for new production facility](source: Abbott Bioresearch Center (Welch, 2003))

*Figure 4* Timeline for antibody project compared to timeline for new production facility

---

8 Source: Abbott Bioresearch Center (Welch, 2003)
Deloitte Consulting used the following figures to compare the net present value for the two scenarios of building a facility for capacity expansion versus outsourcing to a CMO:

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected time to build an average biologics plant (biotech company self-manufactures)</td>
<td>4 years</td>
</tr>
<tr>
<td>Expected time to build an average biologics plant (biotech company outsources)</td>
<td>3 years</td>
</tr>
<tr>
<td>Cost to build an average biologics plant</td>
<td>$400 million</td>
</tr>
<tr>
<td>Average time to reach peak revenues</td>
<td>5 years</td>
</tr>
<tr>
<td>Useful life of a plant to calculate depreciation</td>
<td>40 years</td>
</tr>
<tr>
<td>Effective rate</td>
<td>35%</td>
</tr>
<tr>
<td>Typical gross margin for a biologics company</td>
<td>80%</td>
</tr>
<tr>
<td>Gross margin for a company outsourcing to a CMO</td>
<td>65%</td>
</tr>
<tr>
<td>SG&amp;A as a percentage of sales (company self-manufactures)</td>
<td>20%</td>
</tr>
<tr>
<td>SG&amp;A as a percentage of sales (company outsources)</td>
<td>18%</td>
</tr>
<tr>
<td>R&amp;D as a percentage of sales (company self-manufactures)</td>
<td>20%</td>
</tr>
<tr>
<td>R&amp;D as a percentage of sales (company outsources)</td>
<td>18%</td>
</tr>
<tr>
<td>Initial investment made by the biotech company as a percentage of the cost of the plant</td>
<td>10%</td>
</tr>
<tr>
<td>Cost of capital</td>
<td>15%</td>
</tr>
<tr>
<td>Operating margin</td>
<td>20%</td>
</tr>
<tr>
<td>Post-tax cost of capital</td>
<td>6.4%</td>
</tr>
<tr>
<td>Investment made to remodel the plant for the new drug as a percentage of investment to build a new plant</td>
<td>25%</td>
</tr>
</tbody>
</table>

Table 2 Key statistics for a new biotechnology manufacturing facility

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9 Source: Assumptions as based on the economic valuation model used by Deloitte Consulting to determine the cash flow for a new facility and outsourcing to CMO (Chao & Lakshmikanthan, 2006)
Based on the calculations, the initial investment required to build a facility to manufacture in-house is much higher than outsourcing, which requires the biotechnology company to have the ability to raise high capital. However, for a drug that has high expected peak revenues the company should not outsource as it will not have to pay a premium to the CMO to share the risk. For a drug with expected revenue below $200 million the company should not invest in its own manufacturing facility (Chao & Lakshmikanthan, 2006).

2.1.2 Design

Various possibilities may be considered in the conceptual planning stage, and the technological and economic feasibility of each alternative will be assessed and compared in order to select the best possible project. The financing schemes for the proposed alternatives must also be examined, and the project will be programmed with respect to the timing for its completion and for available cash flows. As the definition of the project objectives and scope has been determined the different types of estimates are required as a project evolves (Barrie & Paulson, 1992):

- **Conceptual Design**: Used to determine whether the contemplated project scope is feasible. Prepared early in the project, prior to engineering design completion. Will incorporate new information from design to obtain an updated estimate of the project.

- **Basis of Design**: Prepared from completed plans and specifications.

- **Detailed Design**: After the scope of the project is clearly defined, the detailed design provides the blueprint for construction. The project cost is forecasted within allowable limits from a combination of conceptual and detailed information. The cost estimate serves as the baseline for cost control. This stage often includes partial contract and other procurement awards.
2.1.3 Construction

As soon as Basis of Design is complete, the construction and procurement phase can begin, depending on the availability of design. This stage needs to be carefully planned and controlled for the delivery of materials and the erection of the project. After the construction is completed, there is usually a brief period of shakedown of the constructed facility before the commissioning and qualification process.

2.1.4 Commissioning and Qualification

The biotechnology industry in the United States is regulated by the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the Department of Agriculture (USDA). The FDA regulates the development, manufacturing and marketing. The term used for the enforced control by FDA of the manufacturing and quality control testing is Good Manufacturing Practice (GMP)\(^\text{10}\). GMP is designed to help assure the quality of drug products by ensuring several key attributes, including correctness and legibility of recorded manufacturing and control documentation. By legislation, the manufacturing facilities are subject to FDA approval and periodic inspection. The GMP regulations affect the architectural and building engineering components of the facility along with equipment and systems. The FDA issued the document International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guide Q7A, which is intended to provide guidance regarding GMP for the manufacturing of active pharmaceutical ingredients under an appropriate system for managing quality (FDA, 2001).

The GMP’s standards are integrated into every activity of construction projects and its conformance is partly determined through the review of documentation done. Some GMP requirements are specific and dictate the use of technology in the facility, while others give room for interpretation. Compliance risks need to be appropriately and proactively managed as incorrect documentation can result in FDA observations of nonconformance, which can delay FDA approvals.

\(^{10}\) For the purposes of the thesis, the terms current good manufacturing practices (cGMP) and good manufacturing practices (GMP) are equivalent.
2.2 Construction Engineering Management

When it comes to organizing the project management throughout a project’s life cycle, there is no single best approach. Among the construction engineering management roles are the project management planning, cost management, time management, quality management, contract administration, and safety management. The owner chooses an approach based on the project and their knowledge in construction engineering management. Each approach has its advantages and disadvantages, and needs to be chosen based on what is beneficial for the particular project, its type, size, and location.

As the biotechnology industry has changed the companies have been faced with the challenge of increasing their focus on cost management. As the new capital projects require high fixed cost, reducing it is often challenging unless novel approaches for the facility strategy are introduced or capital expenditure is deferred, by slowing the project’s progress and thereby lengthening the project timeline. However, new capital projects are often under the pressure from the company’s overall strategy to shorten the project timeline since earlier decisions impose higher risk on the project to change. Thereby, it becomes a challenge to successfully manage simultaneously both time and cost.

2.2.1 Time Management

The timing of initiating a facility project is influenced by the market pressure. Proposed capacity expansion can fall through, due to deferred FDA approval or other impacts on the forecast of expected sales. The owners however, often need to take chances since high R&D investments can be at stake if the production capacity is not available when needed. Various affects, such as failure to be the first mover on the market, and patent expirations can influence the decision. As in other technology intensive industry the trend in the biotechnology industry has been to push for shorter life cycles. Capital availability has enabled the companies to make high investments and sacrifice some cost associated with striving for fast construction in order to keep up with the market drivers.

When pushing for shorter project life cycle, the owners often forego thorough planning and feasibility study and proceed to construction with inadequate definition of the project
scope. Inevitably, redefining the project scope is more expensive after the construction work has started. However, the companies have had to evaluate that risk in comparison with the risk of loss of profit resulting in not getting the product out on the market in time.

Feasibility/Site Selection
Procurement/Engineering
Construction
Start-Up
Validation

<table>
<thead>
<tr>
<th>Projected Timeline</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5 Simplified Gantt chart for the manufacturing facility timeline

The front end planning of the schedule is information intensive, but is highly important and it has been shown that projects that have invested more time and resources in front end planning have proven to be more successful.

### 2.2.2 Cost Management

When organizing the project the owners need to plan the cost throughout the life cycle of the constructed facility rather than only looking at the initial construction cost. Decisions made at the beginning of the project life cycle have far greater influence than those made at later stages (see Figure 6). The design and construction decisions will influence the continuing operation cost and the revenues over the facility lifetime. Small savings during construction may not be worthwhile if the result is much larger operating costs or not meeting the functional requirements for the new facility satisfactorily.

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11 Source: Diagram used in a case prepared at the Keck Graduate Institute of Applied Life Sciences, based on sources from U.S. Bancorp Piper Jaffray, Biogen, and IDEC Pharmaceuticals (Agrawal, Kelly, & Finegold, 2001).
Depending on the in-house capability of engineering and construction management of the owner, there may be a need to seek the expertise of outside professionals to provide adequate planning and feasibility studies. Moreover, by involving the operating management from the beginning of planning stages the owners can ensure that the quality of the constructed facility takes into consideration the cost involved in operation and maintenance.

Owners that have engineering and construction divisions will often treat them as reimbursable, independent organizations. Comparing the cost involved with outside consultants can therefore be misleading, as false economies in reimbursable costs can indeed be very costly to the overall organization. For the owners that do not have the in-house engineering and construction management capability it is important to establish an ongoing relationship with outside consultants in order to respond quickly to requests.

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12 Source: Adapted from a diagram used in a case prepared at the Keck Graduate Institute of Applied Life Sciences, based on sources from U.S. Bancorp Piper Jaffray, Biogen, and IDEC Pharmaceuticals (Agrawal, Kelly, & Finegold, 2001).
Construction projects often involve high uncertainties and construction cost can go way over the estimate based on inadequate scope definition. However, the constructed facility is a success for the owner if it can derive reasonable profits from the operation. It is not given that profit will be higher if construction cost is kept lower, since that can mean having to increase the project duration on the expense of bringing the product to the market at the time needed.

2.3 Contract Administration

After generating enough information for the initial planning of the basis case, the owner needs to decide on the appropriate project delivery method, pricing, and allocation of the project risk to the parties involved in the design and construction phase.

2.3.1 Project Delivery Methods

Facilities construction in the biotechnology industry involves a high degree of technological complexity. The owners are usually deeply involved in the development of

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13 Source: Diagram used in a case prepared at the Keck Graduate Institute of Applied Life Sciences, based on sources from U.S. Bancorp Piper Jaffray, Biogen, and IDEC Pharmaceuticals (Agrawal, Kelly, & Finegold, 2001).
the project, and pick a team of designers and builders with whom they have developed
good working relations over the years. The owner can chose to either select separate
organizations for design and construction, or to select a single organization or a joint
venture to handle both functions.

<table>
<thead>
<tr>
<th>Contract Type</th>
<th>Impact on shorter project completion time</th>
<th>Impact on lower overall project cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separation of organizations</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Integration of organizations</td>
<td>High</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Table 3 Appropriateness of different contract types for different projects

The main factors that the owner uses to decide the appropriate project delivery method
are the size and complexity of the project, the pressure on cost and schedule, and the
owner’s construction management capability.

Separation of organizations

When organizations are separated, one team handles the detailed design, and the project
is then awarded to a separate team that handles construction. In addition, for large
projects the owner may choose to get professional construction management. The most
noticeable effect on the overall project cost and the time schedule for the project using
this type of contract are the following:

- **Schedule:** Design and construction are done consecutively. Due to lack of
  parallel activities this type of contract can have unnecessary lag between activities
  that increases the overall time of the project.

- **Cost:** Since detailed design is completed upon the start of construction, there is
  less need for rework and redesign that can lower the overall cost.
This type of organizing is the most common one, due to the fairness of competitive bidding, but is less desirable when the project is large and complex and when the company requires shorter project time due to market pressure.

The separation of the design and construction team can be undesirable as it leads to isolation of the two teams within the project, where each team looks out for its own interests. Some contracts even have a disclaimer of the responsibilities of the design team related to the details of construction or for on-site inspection. This may possibly lead to the contention of constructability of the design.

Integration of organizations

For large scale projects it has becoming increasingly popular to have one team doing the design and construction\(^\text{14}\). This team needs to have sufficient capability to take the project through detailed designed to a constructed GMP compliant facility. There are different ways to organize this, ranging from the owner doing all the project work, to contracting it all to one firm.

- **Owner-builder operation:** In this type of contract the owner retains full control over design and construction. The owner may choose to handle all work in house or to subcontract part or all of the design and construction process, while still retaining centralized decision making to integrate all efforts in project implementation.

- **Turnkey operation:** In a turnkey contract, all the project work is contracted to a contractor which is responsible for delivering the completed facility based on preliminary design set forth by the owner. This can also include having to operate the facility for a specified period\(^\text{15}\).

\(^{14}\) This type of contract is often referred to as Design Build or Design/Construct Contract.

\(^{15}\) This form of contract is called Build Operate Transfer.
This type of contract is desirable for the following effect on the project schedule and cost:

- **Schedule:** With shorter lead time due to faster hand-off of tasks between the design group and the construction group, this method tends to be efficient in terms of shortening the total time for the completion of the project. Since the contractor is established early on, some construction pre-work activities can proceed concurrently with the design which can result in considerably shorter schedule. This can be done by organizing the construction activities in phases so that each phase can be designed and constructed in a staggered manner.

- **Cost:** This type of contract also removes the friction that can be between the design group and the construction group as in this contract they all work as a team where the design is developed with constructability in mind. This leads to less overall cost, as the team works together to find ways to reduce construction cost with less need for design rework.

However, for this type of contract the owner needs to make sure that quality standards are enforced as the team may be tempted to sacrifice quality to lower the overall project costs or shorten the project time.

### 2.3.2 Construction Contracts

Public biotechnology companies are required to select contractors based on competitive bidding. The rules for the bidding are carefully delineated to place all qualified contractors on an equal footing for competition. Those rules are strictly enforced to prevent collusion among contractors and unethical or illegal actions by public officials.

The detailed plans and specifications are usually prepared by the architectural and engineering firm, which oversees the bidding process on behalf of the owner. The final bids are submitted according to the owner's specifications. The owner uses the different types of contracts to set forth the terms regarding allocation of risk of the project to the various parties involved.
### Contract Type

<table>
<thead>
<tr>
<th>Contract Type</th>
<th>Schedule overrun risk assumed by</th>
<th>Cost overrun risk assumed by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lump Sum Contract</td>
<td>Contractor</td>
<td>Contractor</td>
</tr>
<tr>
<td>Unit Price Contract</td>
<td>Owner</td>
<td>Owner</td>
</tr>
<tr>
<td>Cost Plus Fixed Percentage Contract</td>
<td>Owner</td>
<td>Owner</td>
</tr>
<tr>
<td>Cost Plus Fixed Fee Contract</td>
<td>Contractor</td>
<td>Owner</td>
</tr>
<tr>
<td>Cost Plus Variable Percentage Contract</td>
<td>Owner/Contractor</td>
<td>Owner/Contractor</td>
</tr>
<tr>
<td>Target Estimate Contract</td>
<td>Owner/Contractor</td>
<td>Owner/Contractor</td>
</tr>
<tr>
<td>Guaranteed Maximum Price Contract</td>
<td>Contractor</td>
<td>Contractor</td>
</tr>
</tbody>
</table>

Table 4 Risk allocation for schedule and cost overrun for different contract types

### Lump Sum Contract

The lump sum contract is a one-time payment of money, as opposed to series of payments. The contractor places in the bid the total amount to complete the facility according to the detailed plans and specifications. In case there turn out to be cost savings, they are typically retained by the contractor. Conversely, the risk of cost being higher than estimated is also born by the contractor, and the underestimated cost reduces the contractor’s profit by that amount. This risk is embedded in the contractor’s bid, by placing a higher markup in order to take care of unforeseen contingencies. Contractors however tend to place an accurately estimated markup due to that risk, as overestimating the project may reduce the chances of the contractor to be the lowest bidder for the project. A lump sum contract requires all the design documents to be completed and the entire project construction to be awarded to one general contractor. With this approach the final project cost is known at the start of the construction. However, it does not incentivize the contractor to finish the project earlier and can therefore take the most overall schedule time.

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16 Lump Sum contract is also known as Stipulated Price or Fixed Price contract
Unit Price Contract

For a unit price contract the contract agreement is based on a list of unit prices submitted by the contractor. The payments to the contractor depend on the actual quantities multiplied by the quoted unit prices. This type of contract is common when the quantity of materials or the amount of labor involved in some key tasks is uncertain.

For this type of contract, the owner bears the risk of inaccurately estimating the quantities needed. The contractor however, can price according to own estimates on the quantities. If there is a large discrepancy from the owner’s estimates, the contractor may bid higher unit prices for underestimated tasks and lower unit prices for the overestimated tasks for increased profit.

Cost Plus Contract

In a cost plus contract the contractor receives compensation for the work done, plus some bonus as stated in the contract agreement. For this type of contract there is no incentive for the contractor to minimize the project cost since full compensation is given for actual work done, plus the profit. Risk of cost overruns is therefore fully carried by the owner. The bonus can be any of the following:

- **Fixed percentage**: The bonus can be in the form of a fixed percentage proportional to the contractor’s expenses. This contract leaves little incentive for the contractor to keep down the project cost or to complete the project on time, since every additional unit of actual work is paid for and increases the proportional percentage bonus. This is therefore not a desirable contract method for the owner but is sometimes used when there is a complete uncertainty about the new facility, such as involving new technology or extremely pressing needs.

- **Fixed fee**: For this type of contract the bonus is in the form of a fixed amount, independent of the contractor’s expenses. This method therefore leaves some incentive for the contractor to finish the job quickly as the profit is fixed, but the
risk of cost overrun is still born by the owner as the contractor gets fully compensated for the actual job cost.

– **Variable percentage**: As a way to incentivize the contractor to stay on schedule and to keep the cost down, the owner can have the contractor pay penalty if the actual cost exceeds the estimated job cost, or reward the contractor if the actual cost is below the estimated job cost. The risk of the cost overruns is still assumed by the owner but the contractor has the incentive to keep it as low as possible.

**Target Estimate Contract**

In a target estimate contract, the contractor has the incentive to keep the cost low and to stay on schedule by penalty or reward. The percentage of savings or overrun is usually shared by the owner or contractor as specified in the contract. The contract also states the rewards or penalties for different completion dates

**Guaranteed Maximum Price**

In the guaranteed maximum price contract\(^\text{17}\) the contractor gets compensated for the actual cost incurred plus a fixed fee subject to a ceiling price. Unless the contract is amended with a formal change order, the contractor bears the risk of cost overruns beyond the estimate according to the contract documents. A change order is only made when the owner amends the project scope, not because of price overruns, errors, or omissions. If the cost is underestimated, the savings are either returned to the owner or shared as specified in the contract. For a well defined project, the owner may also have the contractor take the risk of actual project time.

\(^{17}\) Guaranteed Maximum Price contract is also known as GMP, Not-to-Exceed Price, NTE, or NTX contract
3 PART III: New Amgen facility

Amgen’s subsidiary in Juncos, Puerto Rico, called Amgen Manufacturing Limited (AML), was founded with Amgen’s acquisition of the plant in 1992, and started operation in 1993. In 2002 Amgen announced the company’s plans to expand the plant and with FDA’s approval on the first bulk protein manufacturing facility in 2005\textsuperscript{18}, the plant has now been developed as a state-of-the-art facility.

3.1 New Capital Investments

With Amgen’s strong corporate growth the plan for the plant in Juncos was initially set up as for one-time expansion. With such a big capital investment it was highly important to have large engineering resources and establish a large subcontracting network (McCurry, 2006). As with all of Amgen’s global engineering and construction projects, the plant expansion was supported by Amgen’s Corporate Engineering and Capital Projects (CECP) group, which provided technical support and consultancy.

3.1.1 Project Location

Puerto Rico is an attractive location for this plant for several reasons. Puerto Rico is a U.S. Commonwealth and operates under the security of United States laws for customs protection, federal currency and banking, and intellectual property, yet companies do not pay federal taxes until they repatriate profits. This creates an attractive business environment for the biotechnology companies, since their operation in Puerto Rico is taxed locally at a rate of 2-7%, depending on their investment in facilities and the number of jobs created. The initial tax rate is locked in for 10–20 years, and is renegotiated when it expires (Potera, 2007). In addition the companies get 25% credit on purchase of goods manufactured in Puerto Rico, are incentivized for research and development work with trust funds, soft loans, and a 200% special credit for expenditures involved in product or process development. The country’s location, the language\textsuperscript{19}, and access to skilled

\textsuperscript{18} FDA approved the manufacturing facility for bulk production of Neulasta and NEUPOGEN.

\textsuperscript{19} Spanish is the official language of Puerto Rico but the schools have mandatory English classes.
workers are among other important factors in the attractiveness of this location. Due to the high number of biotechnology companies in the Puerto Rico, there is now a good network of international and local companies that are engaged in the plant design, engineering, validation services, packaging, instrumentation, environmental protection and other essential services for the biotechnology companies (Potera, 2007).

The key factors in Amgen’s decision to expand the operation at their plant in Juncos, Puerto Rico have been this favorable business environment as well as the country’s commitment to developing biotechnology manufacturing capability. Throughout the years of operation there, Amgen has built a solid foundation for the plant, and established good relationship with the government in Puerto Rico, the community, and academia.

3.1.2 Plant Expansion Plan

Following the acquisition of the plant in Juncos, Amgen created a long term master plan for the future expansion of the plant. The master plan was based on partial engineering design and included the strategies for cost effective procurement of equipment and material. As part of that strategy, Amgen identified the engineering design and construction companies they had established good working relationship with, and with whom they planned to work to leverage purchases.

The CECP group had the roles to oversee and review the engineering consultant procurement efforts, as well as subcontracts. The plan was strongly focused on cost efficiency, with oversight roles including monitoring overall procurement effort for effectiveness and cost savings, suggesting various program costs saving plans, as well as ensuring that cost efficient subcontracts were being issued by the contractor.

The plant expanded fast from the one building that was operational in 1993 to a state-of-the-art biotechnology facility for bulk manufacturing in 2007, with 16 buildings, totaling 1.2 million square feet, and a fermentation capacity of 225,000 liters. Work force grew from 450 full-time workers in 2002 to about 2,500 before lay-offs began in 2007 (Potera, 2007).
The facility has achieved an outstanding quality and compliance record. The expanded facility includes manufacturing plants, full-testing quality and analytical labs, additional syringe fill and freeze-drying capability and warehouses. It also includes process development facilities, administrative and training buildings, a cafeteria, and a child care center.

3.1.3 Previous Project Planning

The fast expansion of the plant required scheduling and cost estimates that allowed for enough flexibility to enable fast track schedule to keep up with the demand. With the schedule as the main driver, a typical project would be set up as cost plus contract, with risk of schedule overrun assumed by the contractor but risk of cost overrun assumed by Amgen. In order to reduce the overall time schedule, the project phases would overlap as possible, mainly with less detailed design available before start of construction. This required more bid packages and led to higher administrative cost. Risk of changes due to inadequate design was higher which increased the overall project cost. However, due to the nature of the industry at that time, it was considered a priority to minimize the risk of loss of profit resulting in not having full capacity at the facility.

3.2 New Formulation and Fill Facility

The formulation and fill facility is highly important to the Amgen’s operation in Juncos. It is currently in the oldest building at the plant, a building that is over 25 years old and is a legacy structure from the acquisition in 1992. The facility is therefore not built specifically for this operation, and does not fulfill highest standards. This has raised concerns of potential damage to the building, due to external environmental factors such as mold and hurricanes. Analysis of the building indicated a high probability that the plant could experience a significant shutdown. Shutdown of the facility would mean inability to supply major clients and the loss of market share for major products.

About two years ago, Amgen decided to build a new formulation and fill facility to operate in addition to the current facility and thereby mitigating the risk of financial loss in case of a shutdown. As FDA got involved, that soon turned into a project that was
needed for FDA compliance. Throughout these two years, several design alternatives have been evaluated for this new facility and the scope has been altered considerably.

Initially, Amgen had plans to build a state-of-the-art facility, but due to the challenges the company was facing in terms of reducing new capital project expenditure, the team was repeatedly asked to reevaluate the design to achieve maximum cost savings to meet the project needs for FDA compliance. With the drivers of the project shifted so heavily to cost the team was challenged to come up with novel ways to cut cost while still achieving the desired licensure date. Those included considering erecting a modular building or even using an already constructed shell at the plant. With almost two years of design for this project, it was also foreseen that cost could be considerably less due to less uncertainty and less administrative cost. This will also control the project delivery methods used, as fewer bid packages will be needed, typical package will be lump sum, and emphasis will shift to quality management.

3.2.1 Project Organization

Amgen operates this project with an owner-builder type of contract and utilizes single sourcing of key construction and equipment vendors. Architectural engineering and construction management is handled by both the contractor and engineering designer. Other master services agreements are for validation and commissioning. The responsibilities for architectural engineering are consultancy or specialty services as well as equipment procurement. Construction management roles include issuing subcontracts, purchasing long lead material, and purchasing equipment and instrumentation.

3.2.2 Project Scope and Design Alternatives

The project scope has changed considerably since it started almost two years ago. Over twenty change orders have been approved, the number of vial and syringe lines has been decreased, and requirements for operation efficiency have been altered.

During the six months internship a few different design alternatives were considered. The alternatives went through feasibility studies and were presented to Amgen’s senior
management with estimation on cost and time schedule. The following table lists some of the alternatives considered.

<table>
<thead>
<tr>
<th>Description</th>
<th>New stand-alone building south</th>
<th>New-stand alone building north</th>
<th>New stand-alone building north w/spine</th>
<th>Expand existing building</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Temporary parking space south of facility</td>
<td>Finalized parking space north of facility</td>
<td>Finalized parking space north of facility</td>
<td>Already constructed shell as building expansion</td>
</tr>
<tr>
<td>Number of Stories</td>
<td>One-story</td>
<td>Two-story</td>
<td>Two-story</td>
<td>Two-story</td>
</tr>
<tr>
<td>Spine Connection</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Area (Gross Square Feet)</td>
<td>275,000 GSF</td>
<td>264,000 GSF</td>
<td>240,000 GSF</td>
<td>158,000 GSF</td>
</tr>
<tr>
<td>Future Expandability</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk Adjusted IRR</td>
<td>10.9%</td>
<td>10.9%</td>
<td>10.9%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>

Table 5 Different design alternatives for the new formulation and fill facility

Some design alternatives were similar enough to allow for minor adjustment in design, for example when a new stand-alone building was presented at a new location. However, as for other projects, with a considerable change in the scope there is a need for changes in the definition of the process, Process Flow Diagrams (PFDs) and Piping and Instrumentation Diagrams (P&IDs), equipment specifications and requirements, preliminary facility fit, permitting requirements, and any regulatory requirements (Mongiardo & Bobrow, 2005).

When evaluating those different alternatives the main focus was on cost. However, when making recommendations the prioritized factors included evaluating the benefits that
came with having the spine\textsuperscript{20} connected to the building, ability to implement operational efficiency, future expandability at that location, inspection capability within the building, financial risk analysis, constructability, and the fit within the long term site master plan.

The design alternative for a stand-alone building went through the basis of design phase from May 2007 to October 2007. The design team continued working on it although other options were being considered at the same time. However, requests for changes continued throughout the design phase, the design team was decreased, and work was slowed down as much as possible. The actual completion of the basis of design for this stand-alone building ended up being three times longer than originally planned.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8}
\caption{Planned and actual completion of Basis of Design from May to October 2007\textsuperscript{21}}
\end{figure}

As I left the internship, all design options we had been working on had been rejected by the Amgen senior management and a new alternative was being considered. The plant

\textsuperscript{20} The spine is a closed hallway that connects the main buildings. It has both convenience and economical value as employees use it to travel between buildings, or to transfer material and equipment.

\textsuperscript{21} Source: Diagram used in monthly report developed by Jacobs Engineering for November 2007 (Jacobs Engineering, 2007).
had recently acquired more land with the purchase of a nearby plant which opened up for new options. The idea was to build a new building right next to the building that currently houses the formulation and fill operation, but that building had previously been on the edge of the plant’s site. This would allow for the approach to leverage the maximum functionality of the formulation and fill facility, by operating in both buildings and thereby reducing the square footage needed for the new building. Some modifications needed to be done to the existing building, but by utilizing it the need for a CUP building could be eliminated and the sources in the existing building could provide all utility requirements. Basis of Design for this building was scheduled to begin in March 2008.

3.2.3 Project Drivers and Constraints

Building a new formulation and fill facility at the plant has a few constraints. Constraints such as flooding and insurance restriction are needed, as well as location specific restriction such as the following:

- Building classification: Depending on the classification of the building there is a constraint on the hours of fire separation between buildings. Administration building has classification B, manufacturing building F-1, and Warehouse S-1.

- Permitted building height: The allowable height of the building depends on the building classification. A building that is fire rated 1 hour can be approximately 80 ft high, and a building rated 2 hours can be 160 ft high.

- Building mass limitation: Due to the mass limitation at the plant, there is a need to allow a minimum of 120 ft to other Amgen buildings. Building separation within development needs to allow 80 ft between buildings.

- Local Amgen Juncos planning rules: Local rules, Land Use Consultation Document (Junta de Planificacion), set allowable areas for the whole site, including parking etc. This is covered by overall site master plan.

The key project drivers for the new formulation and fill facility are any project element that will have direct impact on the facility operations, construction cost, approval time
line, and compliance. Depending on the design and location, some of the key drivers are the following:

- **Hurricane standards:** The building will need to be designed to resist Category 4\(^{22}\) hurricane. After exposure to the hurricane, the building will require minimal repairs and the production and utilities facility will need to be ready to be placed back into a production mode within 7-14 days of the event.

- **Power and water outage:** The on plant diesel fuel storage can allow for a 3-4 days of manufacturing operation in case of a power outage. The portable water storage allows for 2 days of operation in case of water outage.

- **Capacity:** All plant utilities will follow the N+1 generating philosophy concept. The N+1 generating philosophy is a risk mitigation approach where multiple components (N) will have at least one independent backup component to ensure a 24/7 generating capacity operation in the event of a system failure. To be at a level of N+1, the overall system integrity should not be impacted by the failure of any one component, and should continue to function at acceptable performance levels after the loss of any component.

- **Plant floor design:** All areas of the facility will be designed such that they are accessible for monitoring of any detrimental conditions to the sterile environment, and so that maintenance can be performed without interruption to manufacturing. Where practical, the facility will be designed to have uni-directional product flow so there will be no cross-over of dirty and clean equipment.

- **Fill and finish equipment:** The filling line will utilize either Isolation or RABS technology. This technology is becoming industry standard. It has not been used

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\(^{22}\) The hurricane is of Category 4 when wind reaches 131-155 mph. When wind exceeds 155 mph it is of Category 5. Only one hurricane of Category 5 has hit Puerto Rico since 1852.
at the plant before but FDA is expecting it to be this time. Selection of all equipment will be based on industry proven technology.

3.2.4 Time Scheduling

Design and construction of the new formulation and fill facility was intended to be based on a fast track schedule approach with overlapping project phases. However, nothing was to be bid without being 100% designed.

![Diagram of project schedule]

**Figure 9** High level schedule based on main overall activities from 2008 to 2012

3.2.5 Cost Estimates

As the project design changes, the cost estimates are updated based on the Basis of Design documents. Cost estimates for each discipline, subcontract, construction management staffing, general conditions, and overhead cost are reviewed monthly, but

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23 Source: Diagram used in monthly report developed by Jacobs Engineering in March 2008.
equipment cost estimates are reviewed bi-weekly (Amgen, 2007). The cost estimating process uses change management logs (both approved and pending deviations) to help forecast cost so that all known changes are included in the cost forecast.

When presenting a new design alternative to the senior management, it was considered sufficient to update the cost estimate to a +/-30% accuracy. Although the Basis of Design documents allowed for a +/-10% estimate, such an accuracy was not required until needed for funding submittals (Jacobs Engineering, 2007).

3.2.6 Time and Cost Savings
This project is faced with the challenge to lower cost and defer capital expenditure while still meeting the expected license date and the scope needed. Throughout every design alternative the different cost benefits are evaluated, constructional, operational, the plant's overall site master plan, and the fit to the corporate strategy.

After concerns over cash flow, the whole project was re-planned. The main difference from previous projects was to allow the Basis of Design to be completed as a more formal, standard package, start Detailed Design after completion of the Basis of Design, and start construction after completion of Detailed Design. Equipment procurement was only to proceed as required to support Detailed Design. Cash flow concerns also required the engineering team to limit staffing for the start of the Detailed Design phase. This reduction resulted in a further schedule extension of Detailed Design. Deferring capital expenditure and re-planning the schedule in this way delays the FDA approval.

In order to minimize that delay, changes will be made to the required construction time with innovative approaches such as using modular approach for the facility. This approach has both cost saving benefits and compresses the schedule with shorter design and implementation time, and an efficient approval process. With this prefabricated approach the modular units are shipped ready to build on site. The capital cost savings are mainly due to reduced engineering and construction manpower cost, and with most cost factors pre-defined the risk of cost changes are low. With pre-engineered design the total
design time is estimated to reduce by at least 50%. The construction can happen regardless of on-site progress or conditions and requires less on-site manpower. Conventionally field construction work is around 8 to 10 months but for this modular approach the field construction work can be reduced to 4 to 8 weeks. It will also be cost saving that Amgen has a strong purchasing power from the vendor. With 85% of the work performed at the vendor’s factory the overall capital cost savings are estimated to be approximately 50% (Amgen, 2007).

With Value Engineering the project team has been able to come up with a list of things that if feasible could potentially lower the total project cost. Due to the slow spend approach between design and construction there was a significant float particularly for the interior fit-out packages that could be reduced to shorten the schedule.

3.3 Three Lenses Analysis

This project is challenging in many ways. Not only due to the requirements to achieve the project goal despite lack of capital, time, and senior corporate management support, but also due to the other less defined challenges that the project team is faced with. Changes in the corporate culture call for changes in behavior and even employee attire. The team is intimidated by the worries of losing their job, but also of losing a friend when a coworker is fired. As the company stock price falls, those employees with options worry about the value of their shares in the future. Employees struggle to emphasize the validity of their position for the team in order to prove that they are indispensable for the company in order to keep their job. This leads to challenges in all areas, strategically, culturally, and politically.

3.3.1 Strategic Design Lens

The mission of Amgen Inc. is to serve patients, and that mission is clearly understood by the employees who many work for Amgen Inc. for the personal satisfaction it gives them to know that they are serving patients. The company’s values reflect the same mission (Amgen, 2008):
- Be science-based
- Compete intensely and win
- Work in teams
- Create value for patients, staff and stockholders
- Trust and respect each other
- Ensure quality
- Collaborate, communicate and be accountable
- Be ethical

The project organization chart has around seventy team members but it is divided into thirteen sections, where each section has as few as one team member. In this matrix organization the team members are from different functional departments but report to a single line, while the project manager coordinates the activities of the team members. This form of strategic grouping may have been a good way when all team members were fully utilized but as the work has slowed down it causes confusion and lack of oversight. In addition, lack of communication has occasionally caused a conflict where a few people want to do the same analysis, since the analysis concerns the role of their unit. The project manager has the responsibility and authority to resolve various conflicts such that the established project policy and quality standards will not be jeopardized.

Another challenge that the team faces is that most of the time not all team members are located at the same place. There are a few linking mechanisms used to bridge that. An online extranet has been set up to store all documents related to the project, which connects the team members regardless of their location. Formal linking is in the form of regular status meetings that are held to make sure all team members are on the same page which helps facilitate the flow of information. To encourage informal linking the team usually eats lunch together in the meeting room.

When it comes to making decisions on changes in design it is most challenging to align the different groups and their goals. All groups realize though that they need to present this project in such a way that the senior corporate management prefers. Cost and square footage needs to be minimized, and that can mean having to sacrifice some other
preferences. When presenting a project recommendation the team meets first to discuss it and make sure that everyone is on board. Then, once the phone conference call starts, it is usually the project manager that does the talking to the senior corporate management at Amgen’s headquarters in Thousand Oaks, unless a specialist is needed to cover a certain topic. In that way, whatever the project manager has to present comes as no surprise to the other team members who sit patiently and await the senior corporate management’s verdict.

3.3.2 Cultural Lens

This project is highly important to the operation at the plant and to Amgen as a whole, but at the same time it comes at a difficult time when the company has the strategy not to be spending any money on such capital projects. It has therefore the symbolic meaning of having reluctant support from senior corporate management.

Just like other companies in the biotechnology industry, Amgen has changed considerably since it was founded. Changes are evident in the corporate culture and employees that have worked for the company for a long time have witness it change from leaders who were mainly science-driven specialists to business people that were drawn in from other industries. The visible changes are for example in the appearance of the employees, who used to show up to work in casual clothes but now wear more formal attire. This is challenging as the company tries to translate the science and mission.

Most of the Amgen employees that work on this project are expats. Moreover, majority of those that work full time on this project are based in Conshohocken, PA, where the office of the design engineering contractor is located. When looking at the team through the cultural lens it is clear that it has not managed to create a strong coherent culture. When in Conshohocken the team adapts to the culture of the contractor, and then returns to the culture of Amgen in Puerto Rico when on site.

24 An expat (abbreviated form for expatriate) is the general word used for employees who are temporarily or permanently residing in a country and culture other than where they come from.
With the unstable environment that the project is in, it has become increasingly more difficult to establish a coherent team culture. The expats are feeling at risk of losing their jobs and therefore their meaning to that situation stands in way of the importance they should be putting on the project. Instead of having a common loyalty they tend to prefer to expand their energy in the directions most advantageous to themselves instead of the project team. At times like that it is difficult to keep the team members motivated. To make things even worse, since the project has now spent almost two years on analyzing different design alternatives, the project team has had to redo their work repeatedly. On a regular basis team members would refer to this as feeling like it was Groundhog Day, where the same thing happens over and over again.

With the team members drawn in from different divisions and organizations, it was really important for the project team to learn to work together in order for the project to be successful. During times of stress, some problems of interaction arose when the team members were unfamiliar with their own roles in the project team. Very positive attempts have been made to resolve those problems and improve the team spirit. For example team logo contest, team dinners, and trips to sporting events, where everyone got the chance to bond to further improve collaboration and sense of a common goal.

Despite good attempts to improve the team spirit, there were still some signs of individuals who, due to the pressure of the work on their personal performance and work stability, resisted communication among the team. Those placed obstacles in the way of having effective interventions by all team members and blocked cooperation and coordination. More seriously, they would criticize and blame other members of the group when things went wrong, resent suggestions for improvement, and become defensive to minimize culpability rather than take the initiative to maximize achievements. Those actions were the result of the series of changes the project had been through. What the team members had initially signed up for had changed considerably, ranging from the scope of work to the main work location. Some of them may therefore have had the feeling of false intentions and broken promises. They had signed up for a project that by now should have been far into construction, but after almost two years of work has not
yet been given the green light to start construction. Frustration among team members is inevitable but needs to be dealt with.

3.3.3 Political Lens

The project manager is the most important person the success or failure of the project. The project manager is responsible for planning, organizing and controlling the project. In return, the project manager holds the power to mobilize the necessary resources to complete the project. Even though some coalitions may be formed among team members and their different interests and goals, the decisions are negotiated at team meetings and power base is shared by everyone on the team.

One of the main reasons for why this project is still existent despite the lack of corporate capability to move forward with it has been the project manager’s personal drive. He has exceptional skills to exert interpersonal influence in order to lead the team. His broad knowledge in all areas of the project, coupled with his personality enables him to interact with his team and all the project stakeholders to keep the project alive.
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4 PART IV: Project Development Summary

As this thesis has covered, the biotechnology industry is reaching maturity in its lifecycle and is being faced with increased responsibilities that are tightening the companies’ flexibility in terms of expenditure for new capital projects. The operating environment is expected to remain like that and the companies have already started to adjust by restructuring and altering their project development.

4.1 Effective time and cost management

It is challenging for the biotechnology companies to successfully manage both time and cost. Depending on the project and the company’s capabilities, there are however a few methods that can assist with effectively managing both cost and time. Having the organizations integrated rather than separated enables the owner to have an impact on both shortening the project completion time and decreasing the overall project cost. That enables faster hand-off of task between design group and construction group, and construction activities can be organized in phases with each phase designed and constructed in a staggered manner. The cooperation between the designer and constructor also decreases the overall cost, as they work together to find ways to reduce construction cost and have less need for design rework.

The choice of construction contract type depends on how much of the design is completed before construction award. With staggered construction phases and high confidence in the design, one preferred way for the owner would be to allocate the risk of schedule and cost overrun to the contractor with a Guaranteed Maximum Price Contract.

4.2 Future Challenges

As the biotechnology companies adjust to the new environment of the industry, some challenges will become more prevalent. As in other industries, proper management of the changes will be deciding factor in determining the biotechnology companies’ success in adjusting their project development to the new environment. Effective organizational change management is highly important for the companies to detect trends in the macro-
environment as well as in the micro-environment, and to be able to estimate what impact the changes have on employee behavior patterns, work processes, technological requirements, and motivation.

The biotechnology companies’ main strength is in focusing on research and development and marketing of the products. As the CMO’s have become more advanced, with better understanding of the process in the biotechnology manufacturing, it becomes an increasingly viable option for the biotechnology companies to consider outsourcing the product manufacturing. The companies also seek to lower cost and expand to new markets, which can increase offshoring to counties that offer lower salaries, highly educated workers, and supportive governments.

With increased mergers and acquisitions activities the competitors become fewer and stronger and new organizational challenges emerge. The challenges start with the distraction of the transaction, and continue to the post-merger organization with dealing effectively with the increased number of customers and data, integration of systems, corporate culture, and politics to name a few areas.

The companies in the biotechnology industry have cycled between having too little capacity to having too much capacity. The bullwhip effect of capacity demand will continue to be a challenge for the companies as they build their expansion strategies, due to the increased regulatory challenges to the products in the pipeline on one hand, and increased customer base and market demand on the other hand. As mergers and acquisitions continue this will risk the potential of capacity shortages as majority of the capacity will be concentrated on fewer companies.

The steep learning curve for the companies in the biotechnology industry has however built them up, and their highly skilled and intellectual human capital will remain the companies’ biggest asset. Their passion to work in the industry for the sake of knowing their efforts go to improving the lives of people in real need is what builds the core of the biotechnology companies and despite being challenged with difficult times those values will remain the source from where the companies will draw their strength.
5 References


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