

Process Optimization in Drug Discovery

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Environmental Engineering

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and
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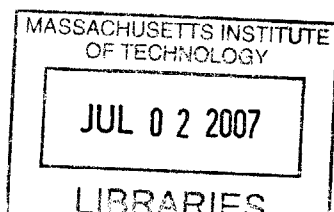
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Abstract

Novartis is one of the largest pharmaceutical companies in the world, with their research headquarters (Novartis Institutes for BioMedical Research) located in Cambridge MA. In this thesis, I explore Novartis's process for developing drugs, specifically the earlier stages of research leading to high throughput screening. During the course of a 6.5 month, on-site project, Novartis's processes were identified, data were collected and relevant literature in product development and organizational structure were surveyed. Based on the accumulation of this information, several opportunities for improvement were identified and from these, recommendations were developed and implemented.

This thesis considers the improvements Novartis could see in their drug discovery process by improving communication between organizations. In particular, I suggest that the company could benefit in cycle time and quality by designing and following more robust lateral processes and by moving their communication mode closer to integrative problem solving.

Following these recommendations, I investigated why Novartis did not already have these processes in place. I hypothesize that the main reason for this is because the research organization at Novartis is focused primarily on exploration, therefore their ability and need to coordinate has not been an area of focus. Novartis has made a very deliberate effort to design an organization that promotes novel drug discovery; perhaps sacrificing cycle time and process efficiency. Because of this strong focus on drug discovery, Novartis has not had opportunity to design and implement efficient processes. By bring in interns from MIT's Leaders for Manufacturing Program, the company is beginning to explore ways to improve their processes without sacrificing their ability to develop novel drugs.

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Chapter One: Introduction

Leaders for Manufacturing Program

This thesis focuses on business process improvements at Novartis Institutes for BioMedical Research (NIBR) in Cambridge, MA, in conjunction with MIT and the Leaders for Manufacturing program. The information in this thesis is based on a 6.5 month internship on site at NIBR and literature in the relevant field. NIBR has chosen to sponsor this internship because the company is interested in applying manufacturing principals to drug discovery.

The Leaders for Manufacturing program at MIT is a dual-degree MBA and Masters of Science in Engineering program focused on manufacturing and operations. The program partners with industry leaders, including Novartis, in order to meld together industry and education. As part of the LFM experience, students each complete a six month internship at one of the partner companies. The topics of the internships vary based on the company's needs and the students' educational interests.

The culmination of the internship is a thesis that melds the on-site learning and project work with relevant literature in the field. The general goal is to synthesize this information in order to develop progressive recommendations for the companies. In addition, students also focuses on the academic side of the recommendations, exploring a hypothesis based on their research.

Project Overview

The executive sponsor at NIBR chose one phase of the drug discovery process as the target area of focus for this internship and thesis. Following extensive research into this phase, three potential topics were identified. These topics included process improvements, physical space, and project transition between teams. Based on criteria recommended by the LFM program, the topic selected was the transition of projects between organizations. Specifically, the subject is to determine the most effective way to manage the research project in order to reduce cycle time in the discovery process.

The project at NIBR utilized a cross-organizational project team to focus on the transition of research projects from one group to the next during the course of the project. It was found that this transition causes both rework and delays in the process; resulting both from variability in the capabilities of the upstream organizations as well as the variability in the processes followed. The project team investigated this transition process and developed recommendations for improving the process. These recommendations are closely aligned with literature in product development and organizational structure.

Research Overview

During the course of this project, there were two areas found where NIBR was not behaving in accordance with widely-accepted literature in the field. The project team's recommendations attempt to address these gaps in their process, while incorporating the literature. The two areas that the team focused on were lateral processes and modes of communication.

Lateral processes are the processes companies follow when communicating between organizations. Literature in organizational structure recommends that companies deliberately develop robust lateral processes that fit the needs of their business. However, NIBR had allowed their lateral processes for this portion of the drug discovery process to develop without much deliberate effort. Therefore, the project team found that this was an area in which NIBR could improve in.

Closely tied to this, product development literature recognizes four modes of communication that occur between downstream and upstream organizations. This literature suggests that for product development, teams employ the communication modes that are bilateral and begin early. During the course of the internship, the project team found that a variety of modes were employed and this was causing many of the communication problems. The team recommended that NIBR move more towards integrative problem solving, a more appropriate mode of communication.

Finally, it is interesting that NIBR has failed to implement these widely accepted principles. The final portion of the thesis explores potential reasons for this; I hypothesize that it is mainly due to the recent formation of the Cambridge site as well as the strong focus on exploration.

Thesis Outline

The following is an outline of the thesis:

Chapter Two: Reviews industry and company background, providing broad reasons why the company chose to begin to focus on improving processes. In addition, the current state for the process is provided.

Chapter Three: Includes the literature review, hypothesis statement and data and methods used to develop recommendations and prove/dis-prove the hypothesis.

Chapter Four: Relates the details of team findings during the course of the project. This includes best practices in existing project team structures, processes and project management among organizations as well as gaps in the current state.

Chapter Five: Makes detailed recommendations for improvement, tying to the literature search, and covers the implementation of these recommendations.

Chapter Six: Revisits the hypotheses to determine if they were proven/dis-proven.

Chapter Seven: Conclusion and summary.

Chapter Two: Industry and Company Background

Pharmaceutical Industry

The pharmaceutical industry is an integral part of the world's economy. Generating over \$489.4 B of revenue in 2005¹, the pharmaceutical industry has made and will continue to make a large impact on life. Global drug development tends to focus on chronic diseases with large patient populations, due to the rising costs of the development process. These medications generally provide long term financial benefit to the drug manufacturer and enable the industry to continue to develop new medications. As in the rest of the medical field, the pharmaceutical industry has been also shifting focus to the elderly as that proportion of the population continues to increase. These are two of the main factors that drive the direction of pharmaceutical drug development.²

One of the key areas of focus for pharmaceutical companies is research in order to develop novel drugs. The pharmaceutical industry spends a tremendous amount of money and time developing new drugs. It costs approximately \$800 million and takes between ten and fifteen years to develop a new drug; it is estimated that the total industry spend in 2005 on research and development was \$51.3 billion. These costs are exacerbated by the low success rate of research, as it is estimated that only one compound out of 5,000 to 10,000 compounds tested results in FDA approval and becomes a marketed drug.³

Success in the brand drug market depends on patent protection. Being the first to market is often critical to the success of a drug, and pharmaceutical companies place high importance on the cycle time of drug development. Once a drug is protected by patent, competitors often find it difficult to enter the market. When the patent has expired, generic drug manufacturers enter and compete with the brand name drugs.

¹ Healthcare & Pharmaceuticals Forecast Americas; Dec2005, p1-76, 80p

² Newton, Nell. *Pharmaceuticals*, Hoovers Online, <http://premium.hoovers.com.libproxy.mit.edu/subscribe/ind/overview.xhtml?HICID=1486>

³ Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2006*, pp. 10, (Washington, DC: PhRMA, March 2006).

Novartis, AG⁴

Novartis is a multi-national leader in pharmaceutical development, focusing on protecting health, curing diseases, and improving well-being. The company's objective is to develop innovative products that will treat patients in order to ease suffering or to cure diseases. The company's headquarter is in Basel, Switzerland and Novartis was formed in 1996 as a result of a series of mergers over the last century.

The company is comprised of four lines of business: Pharmaceuticals, Consumer Health, Vaccines and Diagnostics, and Sandoz (generic prescription drugs). By having both the pharmaceutical and generic division, Novartis is the only major pharmaceutical company with leadership positions in both patented and generic drugs. Novartis continues to grow through development in several key areas: prescription medicines, generic medicines, over-the-counter (OTC) medicines, and vaccinations.

Novartis is financially very successful, realizing a 19.1% net income margin in FY 2005 (pro forma accounting). Their total revenue was \$32,212 million, an increase of 14% over the prior year. Each division was profitable, with pharmaceuticals leading the way.⁵ In 2005, Novartis held the 4th highest amount of market share at 5.00%.⁶

Novartis Institutes for BioMedical Research

Novartis has legally and structurally separated their research organization from their pharmaceutical division, creating the Novartis Institutes for BioMedical Research (NIBR). This division carries out research activities for drug discovery, from Phase D0 to sPOC. The selected for Proof of Concept (sPOC) phase is blended between NIBR and the pharmaceutical division, with responsibilities split based on the project. Following sPOC, the pharmaceutical division manages the remainder of the drug development.

⁴ Novartis Company Website, http://www.novartis.com/about_novartis/en/index.shtml

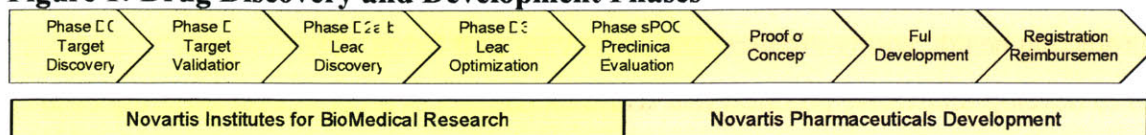
⁵ Novartis 2005 Performance Overview, [e-journal]

http://www.novartis.com/downloads_new/investors/05_Breu_Analyst_2006-01-19_Web.pdf

⁶ DATAMONITOR, Dec. 2006. Global Pharmaceuticals Industry Profile, pp 1 – 16.

Drug Discovery Process at Novartis⁷

Figure 1: Drug Discovery and Development Phases



Phase D0 is the start of the drug discovery process at Novartis. During this phase, scientists identify and validate possible proteins that could be linked to diseases. Scientists generally use genomics, proteomics, modeling and protein function to identify targets. After they have identified a potential protein, the protein is validated – the process that attempts to verify the existence of the protein.

After the target protein has been identified and validated, it will be tested to see what molecules react with, or bind to, the protein. In order to receive output from the test, assays are developed. The assays are developed during Phase D1 and are solutions that house the proteins and tags that are applied to the proteins which will display the reactions compounds have with the target protein. For example, the assay will attach fluorescent tags to the proteins, which enables the scientists to track changes in location and density of the proteins when a compound is applied to the solution.

Once the assay has been developed, the protein is ready to be screened. NIBR utilizes automation referred to as “High Throughput Screening” to be able to test hundreds of thousands of compounds against the protein. NIBR has a compound library of about one million compounds and will test these against each protein to determine if any of the compounds change protein behavior. The scientists have the option of testing the entire library of compounds or can choose a representative subset of compounds to test. This process occurs during phase D2a. The output from this will be a set of “hits” that include all of the compounds that interact with the protein. The quality of the hits varies from sample to sample and the scientist will run secondary screening to determine if the project should continue to the next step in the process.

⁷ Adapted from “What Happens When”; Nov 2005; a presentation by David Roberts, Head, Strategic External Resources, NIBRI

Phase D2b is the part of the process when the scientist will screen hits to determine which ones are viable. This is referred to as hit validation and lead selection. (Once a hit is validated, it becomes a lead and will be further investigated.) The secondary screening is designed to eliminate compounds that will be non-developable or do not process through the cell. Any compound that lacks affinity, potency, selectivity, and efficacy is eliminated if possible. The leads developed from this step are carried forward to Phase D3, Lead Optimization.

During lead optimization, further tests are run to determine the molecule's potential to work in man. At this point, the compound is tested to see if it can travel through an animal disease model to reach the target body location (i.e. kidney), penetrate the cell, and react with the protein. Testing for toxicity is a key component of this stage of testing – this is the final testing process before the compound is tested in man.

Some projects include “Selected Proof of Concept” prior to transferring to the pharmaceutical division. This is usually a very small scale test in man whose purpose is to test for the efficacy of the compound. This has been found to be a low cost way to eliminate targets prior to clinical trials by reliably predicting a lack of efficacy.

At any point during the drug discovery process, a target can be eliminated and drug development for that target will halt. The general process is one of elimination and NIBR strives to eliminate targets earlier rather than later. There is large variability in time devoted to each step, and the success rate of approximately 10% is industry standard.

After NIBR has selected a lead to pursue, and has shown success in animal testing, the project is transitioned to the development organization (usually in pharmaceuticals). The remainder of the drug discovery process (FDA approvals, clinical trials, manufacturing, marketing, and distribution) is handled by the pharmaceutical division with support as needed from NIBR.

*Organization*⁸

NIBR is organized into platforms, disease areas, and support functions, in what is best described as a matrix organization structure. The disease areas (DAs) (oncology, cardiovascular, etc.) focus on a particular disease area or anatomical system. These groups will carry a project through the entire phase of research, until the hand off to the pharmaceutical division.

In addition, NIBR has platforms. Some of the platforms (Developmental and Molecular Pathways, Models of Disease Center, etc.) provide an additional viewpoint in locating targets. For example, Developmental and Molecular Pathways attempts to find targets on a particular cellular pathway. The pathways are believed to be linked to a specific disease and the Pathways group tries to find targets on the pathway. These groups are heavily involved the earlier phases of research, and will generally transition the project to the appropriate disease area after the target is identified and validated.

The remaining platforms provide support to the DAs in conjunction with the work involved in developing drugs. These organizations include Discovery Technologies and Global Discovery Chemistry, and focus on specific activities that are accomplished during phases of the research process. These group's goals are to provide the technology and resources to enable the DA's research. For example, Global Discovery Chemistry works with the DA's to reformulate compounds from the Novartis compound library in order to develop a molecule that can become a drug.

The support functions include finance, HR, operations, and other standard areas that enable business to be conducted at NIBR.

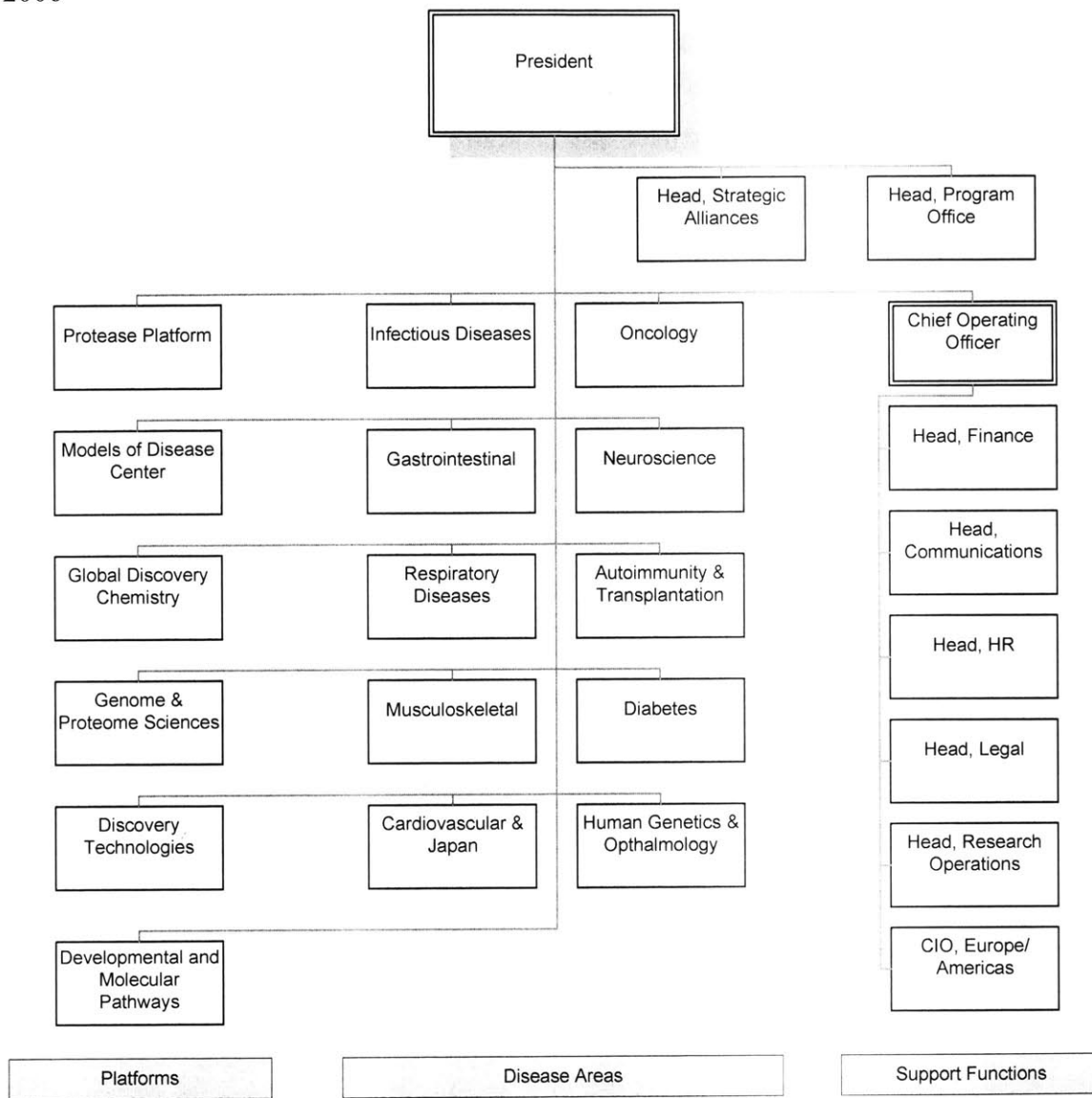
In addition, these organizations are located mainly in Cambridge and/or Basel. Most Disease Areas are only in one of these two locations; but, some of the platforms have

⁸ In January 2007, NIBR reorganized. The data in this thesis are accurate during the time the project was conducted; however some changes have been made since then. These are addressed later in this thesis.

duplicate operations at both sites. For example, Discovery Technologies has screening, assay development, and protein production capacity in both Cambridge and Basel.

NIBR is organized in a manner to encourage high amounts of entrepreneurial activity in order to create novel drugs. They have also centralized functions that perform operations that are more standard across all projects. This should enable NIBR to be able to take advantage of its economies of scale. To date, most of their effort has been to promote the development of new drugs; little work has been done surrounding process improvement. This is expected considering the goal of the organization is to create novel drugs and standardization could inhibit that. However, NIBR has decided that instilling some process improvement should help increase their efficiency; thus providing the impetus for this project.

Figure 2: Organization Structure as of September 2006



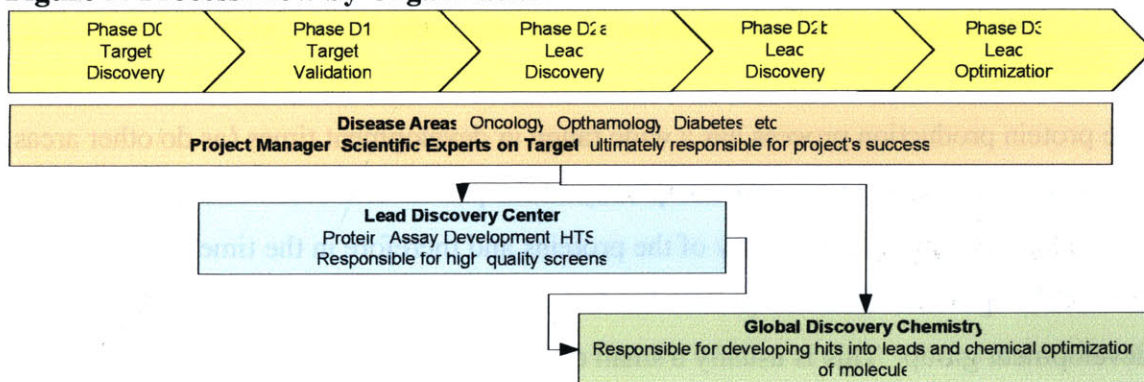
NIBR Team Structure for Research Projects

In order to carry a research project from target selection through sPoC, many organizations are involved. The Disease Areas generally serve as both the project manager and the scientific expert on the target. They are ultimately responsible for seeing that the target gets either eliminated early or promoted through to the pharmaceutical division. In order to accomplish this, they receive support from several other groups.

Discovery Technologies is one of the first groups involved in the project. This organization includes the Lead Discovery Center (LDC), which is responsible for D1 and D2a of the project. The Disease Areas will generally complete some of the D1 work, with varying degrees of work finished prior to transitioning the project to LDC. Once a project has completed D2a, Global Discovery Chemistry becomes involved. This group analyzes the chemistry of the compounds that are leads to maximize the patentability and effectiveness of the compound structure. Their end product is a compound structure that can be provided to the pharmaceutical group to begin developing the drug. External providers are also used in various ways throughout the process.

During the life of the research project, the DA manages the project while relying heavily on support from LDC, Global Discovery Chemistry and others. The organization structure is a blend of centralized and decentralized – the DAs are decentralized and the remainder of the organizations are centralized. This creates unique challenges during the transitions between the decentralized and the centralized organization. For this thesis, the transition in question is between the DA and LDC for D1 and D2a processing. Figure 3 shows the approximate responsibilities between groups and how the projects progress through the organization.

Figure 3: Process Flow by Organization



Detailed Process Descriptions: D1 & D2a

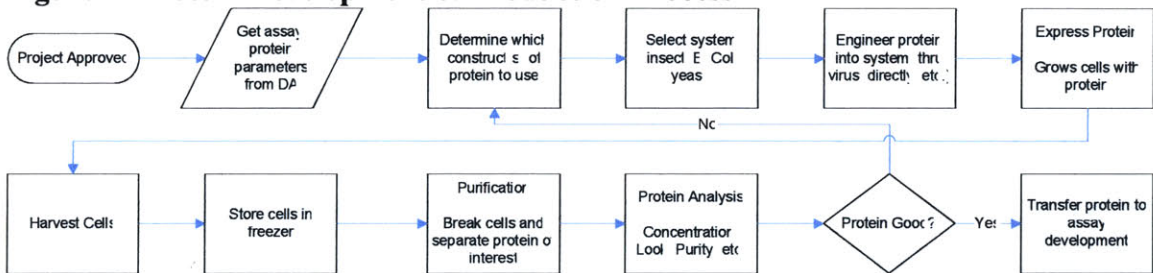
Phase D1

The focus of this thesis is on the D1 and D2a phases of drug development at NIBR. Phase D1 starts after a target has been identified and the project has been approved.

Projects are approved at monthly meeting called “Lead Discovery Project Board” (LDPB) after fulfilling acceptance criteria and gaining support from several areas of the organization. After approval, the next process is to screen the target against compounds to see what compounds react with the target. These compounds are the beginning of the structure of the drug.

Prior to conducting the screens, the company must produce the protein or cell line (target) and develop the assay. NIBR uses both cellular structures and protein in order to run screens; the process for developing a cell line is different for the protein, however the assay and screening processes are the same for both types of screens. Below is the process for producing the protein.

Figure 4: Protein Development & Production Process



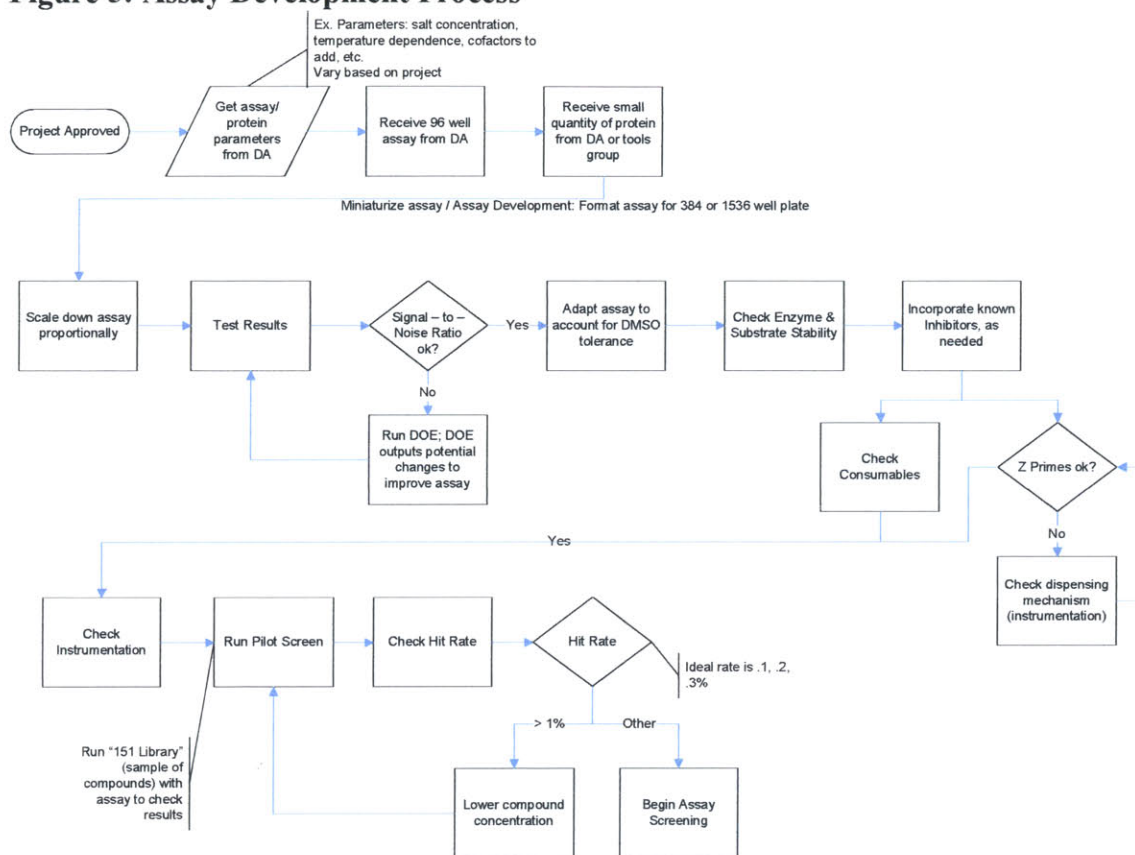
NOTE Protein is produced first in a small batch for testing and then in a large batch for screening. L for 1st batch up to 10CL for 2nd batch

The protein production process has a wide range in development times (as do other areas in the process), depending on the complexity of the protein structure. There is also an increasing trend in the complexity of the proteins and therefore in the time it takes to produce the protein. Once the protein has been produced, it is transferred to the assay development group. This is usually a small quantity of the protein (test portions); a larger batch for screening is made simultaneously with assay development.

In assay development, the lab associates will add reagents to the protein or cells to determine if they will be able to decipher results when the compounds are added to the assays. There are many types of assays that can be produced, and the appropriate type

depends on the target to be tested. This process is very iterative, and also has a high amount of variability in cycle time. The process is shown below in Figure 5.

Figure 5: Assay Development Process



Phase D2b

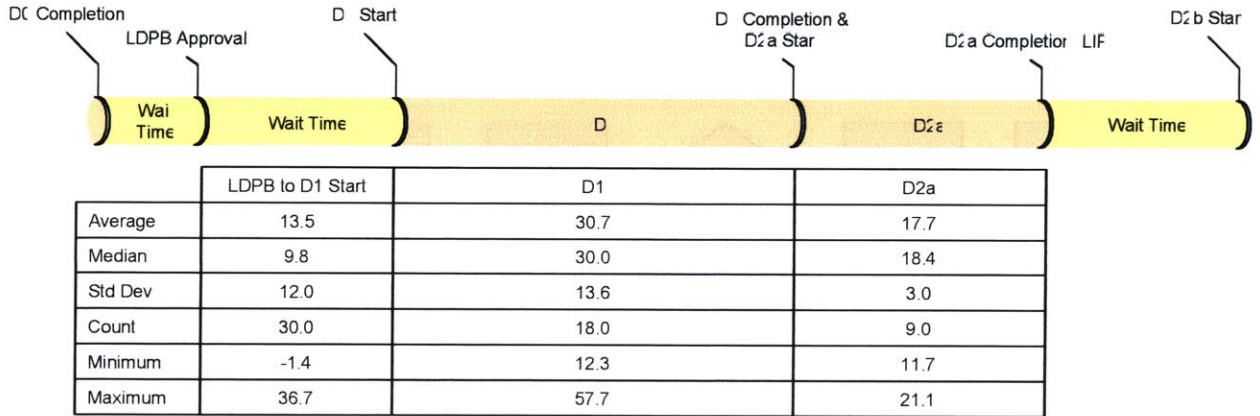
After the assay is produced and the protein/cell is ready, the lab associate begins screening. There is occasionally a wait time before the screening begins, while the associate orders the compounds he wants to screen the target against. There are several types of screens that can be run, and the associates will use different equipment depending on the type of assay. The screening process is either run fully automatic, or partially automatic. This portion of the process has the least variability in cycle times.

Process Cycle Times

Phases D1 and D2b cycle times vary widely from project to project. The average time to complete a project is 13.7 months, ranging between 7.5 and 17 months. This variability

causes difficulty in scheduling and leaves groups waiting for results from the Lead Discovery Group (LDC) dissatisfied with the timeliness of the results. The following high level process was identified to use for creating a baseline of the cycle times for different stages (data is in weeks):

Figure 6: Cycle Time by Phase



Unfortunately, data was not available for D0 Completion to LDPB approval, however it can be assumed that this amount is generally between zero and six weeks because the approval meetings are held at least every 6 weeks. Data was also not available for D2a Completion to D2b Start; anecdotally this amount of time can be fairly significant, and some projects may be cancelled during this period.

It can be noted that the cycle times in each step are not only long, but are highly variable. The longest portion of the process is D1 and the most variable step is the wait time from LDPB to D1 Start.

The wait time prior to D1 Start was quickly identified as an area of opportunity. In order to further understand the reasons for slow/fast starting project, team members were asked to identify why a project was held up or started quickly. Resulting from this information, the top reasons why a project started quickly were:

- The project was high priority
- Resources were available when project was approved

- The DA had been working with LDC prior to the LDPB meeting

Projects were delayed because:

- LDC was waiting for additional information from the DA
- LDC and DA in conjunction decided on scheduling that would delay the project
- There was a lack of capacity in LDC

One key component contributing to the variability in cycle time during D1 is the capabilities and processes between and within DAs. These are different from DA to DA and from project to project, causing LDC to need quite a bit of flexibility in order to handle each project.

Chapter Three: Problem Statement

Project Goal

The goal of this project is to reduce cycle time in the D1 and D2a phases of the research process. NIBR executives chose cycle time reduction as the primary goal because of the potential for reduction in patent protection, pressures to reduce price, the future trends in the industry, the lost revenue that results from the cycle time, and the importance of being the first to file a patent.

Patent Protection

Currently, generic drug manufacturers and governments are attempting to limit patent protection. Governments are investigating the existing intellectual property protection for branded drugs and generic drug manufacturers are contesting existing patents. This could cause the length of time that patents cover brand-name drugs to reduce.⁹

In 1984, Congress passed the Hatch-Waxman Act to provide incentive to generic drug manufacturers to challenge patents. One of these incentives is that the generic drug company will always receive 180 days as the sole generic provider (following patent expiration) if they win the challenge, and sometimes if they lose the challenge. The price during this time period is considerably higher than after more generic manufacturers enter the market. In addition, because of this price reduction, other manufacturers may choose not to enter the market – in essence preserving the higher prices.¹⁰ Generic drug manufacturers only need to spend \$8-\$10 million to develop a drug and have found it very profitable to contest patents. In cases over the last several years, the brand companies won 41.8% of the time, with the generic company winning 36.6% and the remainder of the cases settling (21.6%).¹¹ The risk of generic drug manufacturers contesting patents is increasing considerably; pharmaceutical companies must consider that their patent window could be shortened.

⁹ Healthcare & Pharmaceuticals Forecast Americas; Dec2005, p1-76, 80p

¹⁰ McLean, Bethany, 2007. Party Crasher. Fortune, Vol 155 No. 2, February 5, 2007, pp 37-41.

¹¹ Glass, Gregory, 2005. Patent Attack. Pharmaceutical Executive, April 2005.

Because the patent period is the time when the drug companies' sales for a drug are the most profitable, lessening this window will directly hit their financials. This is one reason that pharmaceutical companies, and NIBR, are attempting to reduce cycle time. Patents are filed very early in the drug development process – at the latest before clinical trials, and usually earlier. Therefore, they want to bring the drug to market as quickly as possible so a higher proportion of their patent window is after FDA approval. Although the portion of the process under investigation is generally before the patent is filed, the pressure to reduce cycle time is carried through all areas of the process.

Time to Market

As in many industries, time to market is a critical component of the pharmaceutical industry. One of the most important parts of this is really “time to patent”; being the first to file a patent often determines whether or not a company will be first to market and sometimes whether or not a company will pursue a particular drug. D1/D2a (target validation and screening) is a large portion of the time prior to being able to file a patent – increasing the case to reduce cycle time.

Pricing Pressure

The increasing availability of generic drugs and pressure from many governments are causing prices to fall. The Economic Intelligence Unit forecasts this trend to continue through 2010. As soon as generic drugs come to market, the generic price is considerably lower than the branded drug price – 20-30% in the first 180 days and can be much lower subsequently.¹²

This creates a pressure on pharmaceutical companies to reduce costs; and correspondently increase revenue. One way the companies can increase revenue is to extend the amount of time during the patent window when they are selling drugs.

Future Industry Business Model

¹² McLean, Bethany, 2007. Party Crasher. Fortune, Vol 155 No. 2, February 5, 2007, pp 37-41.

IBM Business Consulting wrote a report in 2003 predicting that the business model in the pharmaceutical industry will evolve such that, by 2010, R&D time will reduce from 10-12 years to 3-5 years and expenses will drop from \$800 million to as low as \$200 million. IBM expects this to occur as a result of technological advances and continuing genomics research.¹³ While this is only a forecast, it continues to pressure pharmaceutical companies to reduce time and costs.

Selection of D1/D2b

NIBR executives chose D1/D2b as the area of focus for this project because it is a fairly significant amount of time and it was one of the least understood areas of the process. It may not be the largest area of opportunity in NIBR, but is an area that the executive team believes can be improved if it is analyzed. This area does have opportunities to save time and reduce costs, and the executives at NIBR wanted to better understand these.

Each screen costs approximately \$800,000 and NIBR worldwide runs between 60-70 screens per year. The average cycle time for Cambridge screens is 14 months, with a range from 7.5 months to 17 months for NIBR in Cambridge. The \$800,000 costs are mainly due to materials, labor, and depreciation. This is a small portion of total drug development costs, but is not insignificant for discovery. These costs do not include any costs incurred by the DAs during D1/D2a.

By focusing on this area of the process, the costs and time above could be improved. Reducing the cycle time could lead NIBR to be faster to file a patent; cost reduction would enable NIBR to run a larger number of screens with the same costs. However, NIBR executives have prioritized reducing time over reducing costs; therefore, this project will prioritize reducing time over reducing costs.

Literature Review – Product Development

¹³ Breitstein, Joanna, and Al Branch, Jr., 2003. *Marketers Mix*. Pharmaceutical Executive, January 2003, pp. 62.

Wheelwright and Clark have extensive recommendations concerning product development processes and procedures. Many of these are applicable to research in the pharmaceutical industry. Specifically, for the work NIBR performs, product development literature for novel research at the earliest phases is what most closely matches NIBR's business. This research suggests six basic elements of a project management framework¹⁴. These are:

1. Project Definition – defining scope, boundaries, and objectives
2. Project Organization and Staffing
3. Project Management & Leadership – phases, managing tasks, checkpoints/gates
4. Problem Solving, Testing & Prototyping
5. Senior Management Review & Control
6. Real Time/Midcourse Corrections

Wheelwright suggests that these elements should be part of how projects are managed; if not, the project may experience more issues than it would otherwise.

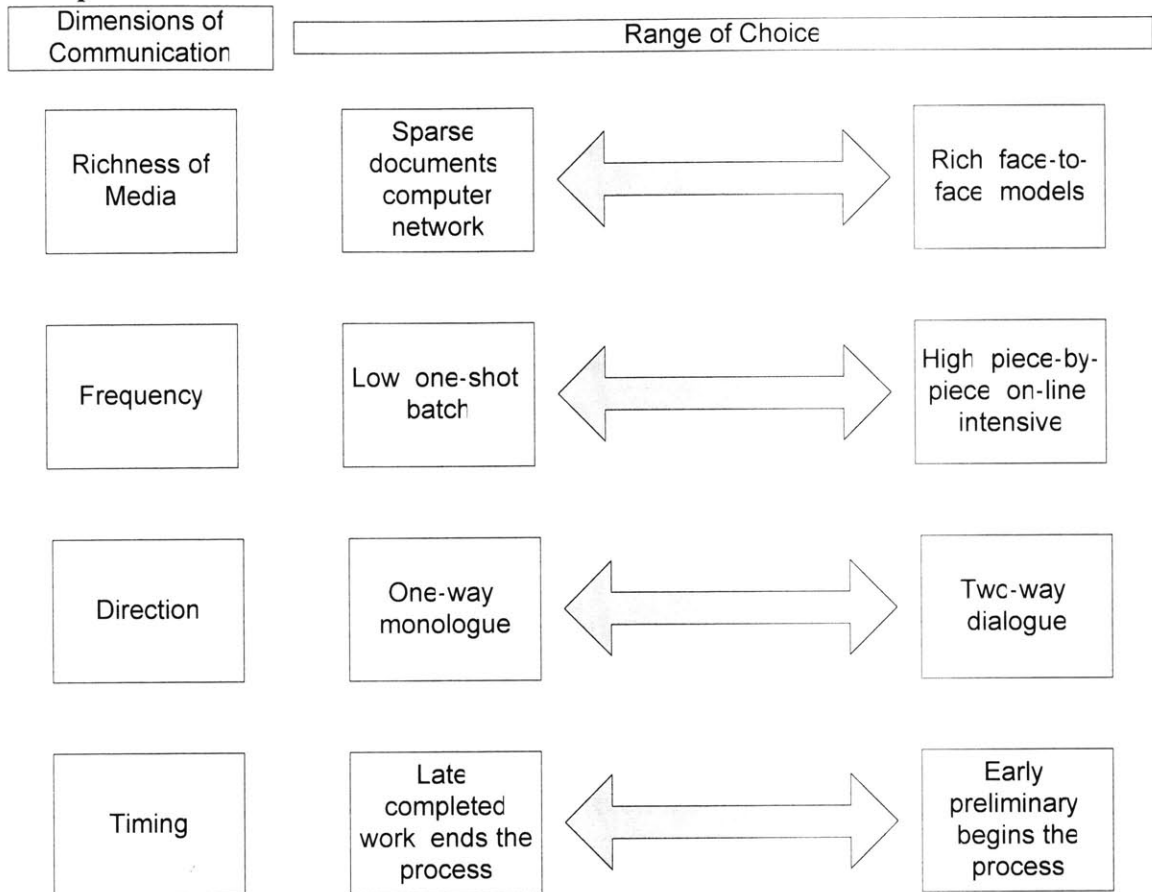
In addition to the project management framework, Wheelwright also recognizes basic principles found in good development processes. These are: maintaining focus on the customer; discipline; detailed coherence across project dimensions; the process must fit with the environment needed for the project; the process should be commonly shared throughout the organization.¹⁵ Both following the above framework and principles, companies can put in place the basics needed for good project management.

After these elements are in place, another critical area of focus is communication between the upstream and downstream organizations (for example, between the Disease Area and LDC). There are many levels of communication, in several dimensions. See Figure 7 for a diagram of options.

¹⁴ Wheelwright, Steven C. and Kim B. Clark. *Revolutionizing Product Development: Quantum Leaps in Speed, Efficiency, and Quality*. New York, NY: The Free Press, 1992. pp.135

¹⁵ *Ibid.* pp 161 – 163.

Figure 7: Dimensions of Communication Between Upstream and Downstream Groups¹⁶



By ensuring the proper level of communication for the project, which should generally be towards the right side of the diagram for NIBR, companies can specify and implement communication practices that are appropriate for their situation. The further to the right a project team operates in, the closer the team is to integrated problem solving.

There are four potential modes of communication based on the above dimensions. These are: serial/batch, early start in the dark, early involvement, and integrated problem solving. Which mode a team operates in depends on when the teams begin to communicate and whether the communication is bilateral or unilateral. Early involvement and integrated problem solving are generally the ones where communication is richer and more frequent.¹⁷ In addition, it is important to note that “true cross-

¹⁶ This diagram is directly from Wheelwright, et.al., Exhibit 7-3, pp. 177

¹⁷ Ibid. pp. 178

functional communication occurs at the working level”¹⁸. In essence, this means that communication is better accomplished associate-to-associate, rather than up one chain of command and back down the other.

Rich, bilateral communication is essential to have integrated problem solving. Integrated problem solving occurs when the upstream and downstream teams work together from the beginning of the project.¹⁹ Both will be taking the other’s requirements and desires into account, preventing rework and missed opportunities. Unfortunately, integrated problem isn’t easy to achieve and demands particular capabilities, attitudes, and relationships to exist in the organization.

The upstream organization needs three particularly important capabilities: downstream friendly solutions; quick problem solving; and, error free design. Downstream friendly solutions mean solutions that are easy to implement for the downstream organization. An example of this is “design for manufacturability” that is common to many manufacturing firms. For NIBR, this could mean the Disease Area designing an assay in a plate that fits into LDC’s automated equipment. Quick problem solving encompasses the ability to resolve differences between the group’s design and the requirements of the downstream organization. And, error-free design will significantly reduce the cycle time as errors caught earlier in the design process are easier, cheaper, and faster to fix than those caught later in the process. For example, it is fairly easy to change the configuration of a molded component before the injection molding equipment has been designed and ordered. However, once that equipment is in house, it can be very expensive to modify.²⁰

Correspondingly, the downstream organization must also possess several capabilities. These are: forecasting from upstream clues; managing risks; and, coping with unanticipated changes. Many times the downstream organization will be required to begin work before receiving the designs from the upstream organization. In this case, it is important for them to possess the skills needed to forecast what the design may be in

¹⁸ Ibid. pp.175.

¹⁹ Ibid. pp.179

²⁰ Ibid. pp. 181 - 182

order to begin working before the design is complete. This is considered forecasting from upstream clues. To aid in this, the organization should also be able to manage risk; they should know what elements of the design are least likely to change and begin working on those first. Lastly, the downstream organization (like the upstream organization) needs to be able to manage conflicts and be able to handle unexpected changes. This last component requires a high level of competence in the people working in the downstream organization. They must be able to quickly process information, determine a solution, and work to implement that solution.²¹

In addition to the capabilities required, the upstream and downstream teams must also trust each other and maintain a sense of joint responsibility for the success of the project. Without this trust, each group will be less likely to help the other group out and the project's success could suffer. In order to develop this trust, the teams should share their tasks, concerns, and ideas with each other. They should allow the other group to see what they're doing (tours of the lab, for example), helping to prove trustworthiness to the other group. Also, Linking the team's goals can foster shared responsibility between the groups. For example, in the case of the DA and NIBR, the goal for both organizations could be a developed protein/cell and assay as well as a screen that has produced leads (or elimination of the target). The combination of mutual trust and shared responsibility ensures that the right attitudes are in place for successful product development.²²

All of these items discussed are important, but how does this actually work? The way the project team is organized and structured will often dictate how work gets done on the project team. After the appropriate resources are in place, with the right capabilities and attitudes, the team has different choices for how to be structured. Several recognized structures are:

1. Functional Team Structure – Work is completed within the functions, and managed by the functional managers

²¹ Ibid, pp. 182 – 184.

²² Ibid. pp. 184.

2. Lightweight Team Structure – Work is completed in the function, and coordinated by an external project manager who possesses little authority over the use of resources
3. Heavyweight Team Structure – The external project manager asserts significant influence over the functions and generally has dedicated resources from the functions
4. Autonomous team structure – The project manager and team members are detached from their organizations to work as an individual unit

Depending on the amount of coordination needed between functions for the project, the appropriate team structure can be selected. When different components of a product can be developed by different functions (windshield wipers and tires), a functional team structure may be used. Lightweight teams are often used when the team members and project leader are committed only part time to the project. This can be successful if the leader is able to influence people to work on the project. However, because the leader does not have direct influence over the team there is a higher probability of failure.

The heavyweight team structure is one that allows for a fully dedicated project team and project manager while still maintaining ties to the functional organizations. The distinction between the heavyweight team leader and the functional team leader is generally that the project team manager acts as the team's supervisors, while the functional manager continues to manage the employees' long-term career development. This is a team structure that has been observed less frequently in practice, but seems to be highly effective.²³ Research evidence suggests that heavyweight team structures promote faster time-to-market, higher productivity, and/or higher design quality. This seems to be due to improved communication, stronger ownership of and commitment to the project, and a focus on cross-functional problem solving.²⁴

However, this can be difficult to implement because of the tension that can arise between the functional team and the project team. One of the possible conflicts occurs when the

²³ Ibid. pp. 195

²⁴ Ibid. pp. 200

functional team becomes envious of additional responsibility the heavyweight team takes on (sometimes outside of the project's scope). This can result in functional teams being perceived as second class citizens and less important to the organization. Another difficulty can be how these teams interact with support functions. Not all team members will be dedicated to the team; if a particular function is only required intermittently, for example, a person may be dedicated only part time. However, the project team could expect that these support functions to give top priority to all of their requests because they are used to full-time support. Finally, some components may not be developed to the technical depth needed to provide the best product. If a technically complex component is developed within a heavyweight team, it may not have as high of a design quality than if it had been developed within a functional team with multiple technical experts. There are several techniques companies can use to mitigate these potential issues before they arise.²⁵

Selecting which type of team is appropriate for the project is also critical to optimizing the development cycle. While heavyweight teams can be quite effective for developing novel products, they can be overkill for small project, such as redesigning a minor component. Therefore, it is often best for companies to develop capabilities of several, if not all, of the team structures. They can then apply the structure most appropriate for each project. This can be difficult to do; companies tend to sway towards a dominate type of structure that becomes embedded in the culture of the company. Companies tend to be dominant towards either functions or teams; a functional organization will find lightweight teams easy to implement and heavyweight teams difficult to implement. The reverse is true for team oriented organizations. The net result of this is that companies need to be able to recognize what their organizational tendencies are and determine what way to best fit their project team structure to their product development needs to their culture.²⁶

²⁵ Ibid. pp. 202-204

²⁶ Ibid. pp. 215 - 217

Literature Review – Organization Structure

NIBR has structured the organization to focus on products. In theory, this type of structure has the benefit of decreasing the time of the product development cycle, encourages innovation and product improvement, and allows broad operating freedom. However, there are also negative impacts to this type of structure. These include divergence (lack of information sharing between organizations), duplication of effort between organizations, and lost economies of scale.²⁷ NIBR has attempted to combat this by including some support functions, such as LDC, as centralized operations to support all the product groups. This is a recognized method to enable economies of scale in a product organization structure²⁸.

In any organizational structure, one of the key capabilities required is the company's lateral capability. Galbraith defines lateral capability as an organization's "ability to build, manage, and reconfigure ... various coordinating mechanisms to achieve its strategic goals". There are five type of lateral capability: networks, lateral processes, teams, integrative roles, and matrix structures. The first two of these, networks and lateral processes can happen naturally, while the last three are deliberately created. Companies choose which of these to develop, and how, to best fit their business and organizational strategies.²⁹

Networks are fairly self-explanatory, they are simply the relationships people build with each other both at work and outside of work. In an organization, they can be formal relationships, such as customer to supplier or manager to subordinate, or they can be informal relationships. Networks will naturally form as people meet each other; although companies can do more to encourage them if they desire. Some practices to help develop networks within an organization include co-locating people who will work together,

²⁷ Galbraith, Jay, Diane Downey and Amy Kates. *Designing Dynamic Organizations: A Hands-On Guide for Leaders at All Levels*. New York, NY: AMACOM, 2002. pp. 71

²⁸ *Ibid.* pp.71.

²⁹ *Ibid.* pp 136 – 173.

starting extracurricular groups (such as a women's network) for employees, meetings and retreats, training programs, and rotational assignments.³⁰

Lateral processes will also form naturally, but may not be as effective as ones that are deliberately put together. These are the processes that enable organizations to work together – for example regular cross-functional team meetings. Lateral processes dictate how information is shared and decisions are made when coordinating activities that cross organizations. Processes will informally develop, but they should be formalized and documented. The trick is to continue to evolve them over time so that they meet current business needs and don't become overly bureaucratic.³¹ This is an example of when lean manufacturing can be applied to business processes to encourage continuous improvement. Many of the recommendations from this thesis center around developing and refining lateral processes between the DA and LDC.

There are many types of teams that are formed in today's workplace. These include issue team, created to correct a particular issue, work groups that are groups of people who perform similar work but do not depend on each other to complete their jobs, and cross-business teams. Cross-business teams are the ones at NIBR that are the subject of this thesis. These are what they sound like – groups of people from various organizations working on a particular project.³²

In order to further bring together organization, integrative roles can be used. These are people in managerial, coordinator, or boundary-spanning roles whose responsibility is to work across organizational departments without formal responsibility. The main goal of these employees is to ensure that each component of work fits with the overall strategy of the organization and to optimally leverage and coordinate resources among units. This will generally be accomplished through sharing information among groups and being adept at tying together disparate sources of information into a cohesive picture.³³

³⁰ Ibid. pp. 141-150

³¹ Ibid. pp. 151

³² Ibid. pp. 156

³³ Ibid. pp. 165

Finally, if the above techniques aren't enough to pull together a product and functional picture, a matrix organizational structure can be used. These structures generally have senior leaders focused on either products or functions and the layers below these leaders reporting to both groups. This dual reporting structure introduces complexity into the relationships and incentives and can be challenging to manage. This difficulty has led Galbraith to recommend that companies employ this structure sparingly.³⁴

Hypothesis Statement

This thesis will focus on how lean manufacturing principles can be applied to the project management, team structure, and processes of the D1/D2a research team, focusing on the transition from the DA to LDC organizations. This is not a traditional use of lean principles, and it will be challenging to bring this mindset to a business process.

Based on the widely published literature on concurrent engineering and best-in-class product development, I hypothesize that if Novartis doesn't manage their product development in a manner consistent with product development literature, the average cycle time and cycle time variability will be longer than necessary. Specifically, given that literature is very clear on the issues that can occur when transitioning work between organizations, NIBR will also have these same issues. In addition, practices that are recommended in literature to improve these transitions can also aid NIBR in their processes.

Literature points to the conflicting goals of exploitation versus exploration. Essentially, when an organization is focused on one, it has difficulty with the other.³⁵ NIBR is a classic example of an exploration strategy, which is the correct strategy for a research organization. The expectation for this type of strategy is that the coordination may be lacking as a result of the focus on entrepreneurial activity encouraged by the organization. However, when an organization is focused on exploration, their processes

³⁴ Ibid. pp. 172

³⁵ March, James G, 1991. Exploration and Exploitation in Organizational Learning, *Organization Science*, Vol. 2, No. 1 (Feb 1991), pp. 71-87.

are generally less efficient and this can result in longer cycle times. NIBR is now considering how to integrate some efficiency and coordination into their organization, without sacrificing entrepreneurial energy.

While determining what the best strategies are to increase coordination, it is useful to also examine why NIBR has failed to coordinate effectively. There are many typical inhibitors to coordination, and I hypothesize that two of those that have impacted NIBR are:

1. The organization in Cambridge is newly formed and staffing ramped up very quickly (1.5 years to hire the majority of the staff), causing the networks and lateral processes to be underdeveloped. I hypothesize that NIBR has underdeveloped networks mainly due to the length of time the organization has been in existence and the rapid hiring of employees. Over time, these relationships should be formed, producing a better lateral capability for NIBR. The downside towards this could be if a high percentage turnover persists. The region that NIBR is located, Cambridge MA, also houses many other biotech and pharmaceutical companies and competition between companies for key talent can be rigorous.
2. The organization is structured based on products, and the incentives are very strongly aligned with developing novel drugs. I further hypothesize that the organization is so strongly focused on product development that it has neglected to develop its process capabilities.

The literature available on organizational structure and best practices in product development, provide an objective viewpoint with which to assess the hypothesis. In addition, a robust analysis of the current state at NIBR was performed.

Data, Methods, and LFM Project Team Structure

In order to prove/disprove the above hypothesis, I needed to determine what NIBR's current processes were and what the gaps in the process were that could lead to issues. These gaps could be used to find particular root causes of problems and furthermore to

recommendations for improvement. To manage this project, I organized a small team. This team included representatives from three disease areas (Cardiovascular - CV, Diabetes & Metabolism - DM, and Developmental and Molecular Pathways - DMP) and a representative from LDC. The DAs that participated were selected based on the input of executive management as well as their interest level in the project topic. The participation was fantastic, with each team member getting involved well beyond what was expected of them by NIBR management.

My project plan was to follow the DMAIC Six-Sigma process. This acronym stands for: Define, Measure, Analyze, Improve, and Control. This method is outlined in many literature sources, and is also used in corporate training courses. One source of this method is prescribed by Mike George, et. al., in What is Lean Six Sigma?. George's book provides an overview of lean manufacturing and six sigma and also covers common toolkits used by companies implementing and sustaining lean manufacturing in their corporation. While many companies that utilize these principles are focused on operations, the same principles can be applied to non-traditional environments to improve processes. George covers four keys to lean manufacturing that served as the guide to our project goals: "Delight your customers with Speed and Quality", "Improve your Processes", "Work Together for Maximum Gain", and "Base Decisions on Data and Facts". Combined, these foundations serve as a great guide for implementing lean manufacturing on both a large and small scale.³⁶

The project definition work was completed by mapping out existing processes, interviewing employees within LDC, and analyzing the available data (prior to the formation of the project team). This stage of the process led to the project selection of evaluating the transition of projects from Disease Areas to LDC.

The first step with the project team was to measure the current state. The crux of this was completed by holding process mapping workshops with each of the participating

³⁶ Georges, Mike, Dave Rowlands, and Bill Kastle. "What is Lean Six Sigma?". New York, NY: McGraw-Hill, 2004.

groups to identify the current process while noting issues and best practices. The data analysis from the prior step was also carried forward to this step.

Next, as a team, we analyzed the results from these workshops. I consolidated the results into process maps (see Appendices A-D) and categorized best practices and issues (see Chapter Four: Best Practices & Areas of Opportunity). Then, a meeting was held among the core team as well as some additional team members who were interested in the project. During this time, these results were analyzed. Each group presented their organization's processes, issues, and best practices. This enabled quite a bit of learning for the team and began the analysis. Following this meeting, we identified and prioritized the most critical issues to try to fix.

After the top priorities were identified, I worked with several others to develop the recommendations. The first was a new process to be used to manage the transition, the next was a checklist to help coordinate roles and responsibilities, and the last was to create training documentation. These three recommendations were finalized and approved by the project team.

At the closure of the project, the implementation had begun with a pilot of one project which was quickly followed with other projects. During the pilot, the recommendations were adjusted as needed and the new process is being rolled out on all new projects.

A large portion of the project work consisted of education of the team members. The team members were all scientists, with varying understanding of each other's groups and of process improvement. In general, familiarity with process improvement methods, such as lean manufacturing, was quite slim. At best, some of the team members were process-minded and intuitively understood efficient processes, but had very little formal training. Because of this, a lot of the meetings centered on educating the project team on how to map out current state processes, what to look for in those processes, how to design a more efficient process, and what the benefits are of a more efficient process.

The process mapping sessions proved to be an excellent technique to illustrate what a “process” is and how it applies to drug discovery. There was initially confusion among the team about what was process and what was science. Some team members recognized that they followed a fairly regular process, while others felt that every project was handled differently. For the latter group, they were usually confusing science with process – different assays and targets (science) were thought to be processes. The process mapping sessions helped to clarify this distinction and enabled the project team to begin to recognize gaps and make recommendations.

After completing the process mapping, the identified best practices and areas of improvement (see Chapter Four) provided the team with areas to investigate after the conclusion of this project. It also enabled some quick wins that each area was able to implement immediately. For example, LDC was previously scheduling projects based on lab head input. Following a process mapping workshop, associates took over this responsibility as it was determined that they were closer to the process and better able to assess the schedule.

In addition to the core team members, associates were given the opportunity to participate in the project. This is a critical component to any process improvement effort, and one that contributed highly to the project’s success. The associates participated to varying degrees; one of the recommendations was managed by two associates, while other recommendations included associates in the decision making. This served several purposes: the recommendations were generated by the people who know the most about the process; buy-in was gained from the associate population; and the associates involved were able to learn a new skill.

Last, the Disease Area representatives were not very familiar with each others’ areas and spent time sharing information about how they managed projects, what resources they used, and how they saved time during a project. This proved to be quite valuable; one of the disease areas decided to add more formality to their project management structure, another began to run small scale screens, and the third utilized an additional resource for

screening. These may not have been entirely linked to the LFM project, but it probably had some influence on these decisions.

Chapter Four: Best Practices & Areas of Opportunity

The transition from decentralized organizations (DAs) to one centralized organization (LDC) has a high impact on LDC's performance. After the DA has selected a target that it sees as an opportunity for a novel drug, LDC is responsible for testing which compounds will change the behavior of the target. The way this transition is managed varies greatly between Disease Areas and within each DA. This creates some of the variability that LDC sees. For example, some projects will come to LDC with most of the assay development and protein/cell development (D1 activities) complete, while others will come in with virtually zero D1 activities complete. LDC generally does not know what state they will be receiving the project in until they see the project in the LDPB meeting. This makes it difficult for LDC to manage their resource allocation and impacts their level of service to all DAs. It also contributes to the wait time prior to the project beginning if LDC has to request additional information from the DA.

This transition can lead to work being performed in silos – the DA performs certain activities while LDC performs others. The communication between groups during this time may be limited, sometimes resulting in rework and assays that don't meet the other group's scientific specifications. Because there is not always regular communication, the end results of D2a can be negatively impacted. The hit lists produced are not always used by the DA, sometimes because the project was cancelled due to target invalidation or deprioritization during the process. Or, the DA may not be prepared for the next step when the hit lists are ready.

On the other hand, when communication between LDC and the DA is well managed and the roles and responsibilities are clear, this is reflected in shorter wait times, less rework, and higher quality results. In these cases, the DA generally works with LDC prior to the LDPB meeting and will keep in contact with them throughout the project. LDC has also been working to improve this relationship by assigning lab heads to be "DA Coordinators" whose responsibility is to communicate with the DA and to serve as a resource and central point-of-contact for the DA.

In addition to the data in the prior chapters, the following issues and best practices were identified. During the process mapping workshops, the main finding was that each area has very similar processes, but the difference is in how each step is resourced. The difference in resources reflects the varying levels of capability between the groups; one group had very little assay development or protein production resources, while the other two had very well developed resources in these areas. The group that had the least amount of capabilities relied the most heavily on LDC and also formed relationships with external vendors to complete early phase research work. The other two groups also utilized LDC, but not to the extent that the first group did. (The process maps from these are in Appendices A-D and the areas of opportunity and best practices are below.)

Areas of Opportunity

There were several common areas of opportunity identified, and many unique to a particular group in the workshop. Below are several tables consolidating the areas of opportunity. The tables also include whether the areas were in scope, out of scope, or an item to keep in mind while developing recommendations.

Table 1: Areas of Improvement - Resources

Action	Description	Potential Impact
Keep in Mind	Layout Lack of space	Disorganized work space
Out of Scope	Information It is hard to get information about other DAs projects	May repeat work
Out of Scope Keep in Mind Try to Fix	Equipment Certain pieces of equipment break down frequently (SelecT, HTS, etc.) Equipment requires a high level of maintenance DM does not have access to get small compound libraries to run screens	Downtime; throws off schedule Associates spend time on non-value add activities Unutilized equipment, lost opportunity
Keep in Mind Try to Fix	People Structural Biology & BMP lack resources to fill all needs CV does not always have ready access to assay development/tools skills	Valuable experiments are not run; long wait time if using these groups Longer cycle time; more wait times when transitioning to other groups

Table 2: Areas of Improvement - Process

Action	Description	Potential Impact
Try to Fix Try to Fix Keep in Mind Try to Fix Try to Fix Try to Fix	<p>Scheduling/Cycle Time</p> <ul style="list-style-type: none"> • Wait time between hand-off of assay/tools & start of work in LDC • LDC schedules are not accurately forecast (usually underestimated) • Scheduling is difficult because of the variability in cycle time • Time to transition projects to LDC seems high • There may be more of a wait time if Mass Spec is used • Tools Development/Production highest variability in work content & time 	<p>Increased cycle time</p> <p>Makes planning difficult; undermines LDC reliability</p> <p>Contributes to above</p> <p>Increased cycle time'</p> <p>Increased cycle time</p> <p>Difficult to predict time, potential for waste</p>
Try to Fix Try to Fix	<p>Redundant Work</p> <p>LDC is redoing some work</p> <p>Practicality of assay/tool from DA may not meet LDC's needs (\$\$, steps...)</p>	<p>Increased cycle time</p> <p>Increased rework</p>
Keep in Mind	<p>Planning</p> <p>High amount of emphasis placed on HTS, may push out other types of screens</p>	<p>Potentially increased cycle time to D2b</p>

Table 3: Areas of Improvement - Soft Areas

Action	Description	Potential Impact
Try to Fix Try to Fix	<p>Communication</p> <p>Ad-hoc communication between LDC & DA is inconsistent</p> <p>Problems encountered in LDC are not communicated to DA in a timely manner</p>	<p>Lost information; potentially redundant work</p> <p>DA could have solution that would have helped; causes distrust</p>
Try to Fix Try to Fix Keep in Mind Try to Fix	<p>Incentives</p> <p>DA priorities are not always in alignment with LDC (#/screens vs. #/D3's)</p> <p>LDC's current metrics do not tie to project success</p> <p>There are different priorities in DAs for use of screens</p> <p>Screens are not always picked up by DA</p>	<ul style="list-style-type: none"> • Creates a source of tension; could cause non-value added work • Lack of ownership for project in LDC • Creates problems when prioritizing between DAs • Time/resources spent on work that's not used
Try to Fix Out of Scope	<p>Team</p> <p>LDC-Only meetings exclude DA for decision making and problem solving</p> <p>Unequal division of labor for LDC associates during wait time</p>	<ul style="list-style-type: none"> • LDC not utilizing valuable resource; degrades relationships • Decreases productivity of group

After compiling these, each areas was assigned a priority of “Out of Scope”, “Keep in Mind”, or “Try to Fix”. For the “Try to Fix” items, these were further analyzed to enable them to become either “In Scope” or “Keep in Mind”.

The team assessed each area and used a criteria matrix to guide the recommendations and solutions. There were many potential avenues that the project could have taken, but only one direction was chosen because it had the largest impact on the highest priority issues (see pp. 48).

Best Practices

Also during the process mapping workshops, the teams identified best practices. These best practices were defined as something they thought worked well that either their group did or that they had seen or heard of in other groups/organizations/companies/etc. These serve as the baseline for both the development of the to-be process map as well as recommendations. The tables below reflect the best practices.

Table 4: Best Practices - Resources

Description	Potential Impact
<p>Equipment/IT - LDC</p> <ul style="list-style-type: none"> • Cherry-picking capability in Cambridge • HTS allows processing overnight, BUT... • Better maintenance of equipment • On-line tutorial for screening 	<ul style="list-style-type: none"> • Reduces cycle time for CA orders • Decreases cycle time • Reduces break-downs • Lessens learning curve
<p>Equipment - DA</p> <ul style="list-style-type: none"> • High capacity of equipment • High variety of equipment • Small-scale screening equipment available for tools/assay development • High flexibility (workstation-type) & capacity in DMP screening group • Use LDC-compatible equipment • Standardize equipment throughout company; retain flexibility • Hire a central maintenance group for NIBR Cambridge • Determine what capabilities each group has 	<ul style="list-style-type: none"> • No waiting for equipment, but higher cost • Variety of experiments/options • Labs develop higher quality assays, can use this info to develop leads • Can change between screens rapidly, less wait time for small-scale screens • Reduces adapt-to-equip. time • Easier to maintain, could negotiate better pricing, compatibility between groups, difficult to implement • Takes workload off associates, perhaps faster to repair equipment • Enables knowledge sharing between groups
<p>People</p> <ul style="list-style-type: none"> • Project teams in DA are capable of developing assays and tools • Increase headcount in areas needed (structural biology, BMP, etc.) • CV – more access to people with assay development & tools skills • Receive help from LDC for non-HTS screens/assay dev./tools • Increase cross-training of LDC employees; incorporate mentoring to reduce cycle time impact • Increase FTE's on difficult programs 	<ul style="list-style-type: none"> • Higher ownership of project in DA, allows screening group to run with less variability • Decreases wait time, enables more use of these activities • Decreases wait time & work time • Enables DAs to use LDC skill set for needed tasks • More flexible staff enables less wait time • Reduces cycle time
<p>Materials</p> <ul style="list-style-type: none"> • LDC stockroom is good supply source; could be better utilized 	<ul style="list-style-type: none"> • Reduces non-value add work & cycle time; difficult to maintain

Table 5: Best Practices - Process

Description	Potential Impact
<p>Project Management</p> <ul style="list-style-type: none"> • Gated, formal project management process • Plan in advance & include downstream activities in plan (D2b+) in initial planning • Tracking tools schedule in a database • Allow/Incentivize DA to cancel screens • Tighten LDPB approval requirements while still allowing flexibility • LDC to provide DAs with information to enable the DAs to build “LDC” compatible assays/tools/etc. • Improve scheduling in LDC • Determine a way to prioritize projects within LDC queue vs. FIFO processing 	<ul style="list-style-type: none"> • Process is predictable, easier to train new employees, ensures steps are not lost • Keeps big picture in mind, ensures all activities will tie together in end • Allows better forecasting/scheduling • Reduces non-value add activities • Reduces variability in LDC processing times and enables better scheduling • Reduces rework; makes transition to LDC smoother • More predictable process, better able to evaluate resources • Most important projects will be worked on first; may be difficult to prioritize
<p>Order of Operation</p> <ul style="list-style-type: none"> • Tools – choosing & testing multiple constructs and systems simultaneously • Ensuring the next group in process will be available prior to starting a task • Do bio-physical characterization early in the process • Have hit triaging strategy & secondary assays ready before screen is complete • Starting D1 activities while waiting for LDC • Have an LDC rep at the DA D1 Approval meeting • Have LDC work with DA earlier in the assay development process 	<ul style="list-style-type: none"> • Reduced time to D2b, but could increase work load • Avoids starting work that will not be finished; helps with scheduling • Know assay better, will be necessary when problems are encountered • Reduced cycle time; helps maintain momentum while waiting for screen • Reduced wait time; need to avoid rework • Shares valuable knowledge before work starts • Less rework
<p>Project Strategy/Science</p> <ul style="list-style-type: none"> • Prior to running/developing an assay, determine what it will be used for • Develop very “deep” assays • Develop assays based on screening needs • High consistency of assay quality/format/process in LDC • Use the first good assay to run screens • Keep cell/assays in production (in DA) • Use data from pilot/testing screens to find hits • Run several types of screens, starting simultaneously if possible • Utilize alternate, non-HTS lead finding activities more frequently & earlier in the process • Find out what DA can do to help LDC while waiting for a project to start • Allow DA to update assay in LDC process without redoing LDPB Approval 	<ul style="list-style-type: none"> • Prevents running “interesting” assays and focuses on “decision-making” experiments • Better quality assay & screen results • Reduces rework • More predictable output, allows flexibility in scheduling • Reduced cycle time, could be higher cost • Eliminated start-up/shut-down time, \$\$ • Could get to D2b faster, makes testing screens more useful • Reduced cycle time to D2b if shorter screens result in hits • More leads, faster to leads • Reduces cycle time & wait time; need to avoid redundant work • Reduces cycle time

Table 6: Best Practices - Soft Areas

Description	Potential Impact
<p>Communication</p> <ul style="list-style-type: none"> • Regular cross-functional project team meetings • Ad-hoc & formal meetings within organization; help from peers • Ad-hoc & informal meetings with LDC • DA coordinator role within LDC • Provide feedback from DA to LDC post-screen on project progress • Provide feedback from DA to LDC on DAs progress towards secondary assays, chemistry, etc. 	<ul style="list-style-type: none"> • All forms of communication keep project continuity • Allows easy access to peers for problem solving, knowledge sharing • Gives DAs single point-of-contact • Increases ownership in LDC for projects, increases learning • Enables LDC to better align their schedule with the DA
<p>Incentives</p> <ul style="list-style-type: none"> • All groups are tied to project's success • Incorporate point system for LDC to align incentives with DA – include non-HTS activities & provide higher credit for harder assays/tools/screens 	<ul style="list-style-type: none"> • All groups held accountable; eliminates “free riders” • Allows LDC to get credit according to level of difficulty and for activities that don't lead to screens; enables LDC to provide services in demand
<p>Team</p> <ul style="list-style-type: none"> • Screening, informatics, chemistry, etc. involved at beginning of D1 & embedded in the project team • Peer review of project at beginning of project, within org & between DAs • Associates empowered to own their projects • Cooperation between groups within organization high • Include LDC in DA meetings & vice versa 	<ul style="list-style-type: none"> • Less rework; generates buy-in and ownership for project for all groups; keeps all groups on same page • General knowledge sharing, higher quality, faster results • Job satisfaction, decision making authority with people who have the knowledge • Knowledge sharing, etc. • Knowledge sharing & increased team building

Overall, the “soft” and “process” best practices that were found during the process mapping workshops relate to the earlier literature. These best practices were more tactical than what was studied in literature, but do generally follow the literature recommendations. For example, the DA Coordinator role was mentioned as a best practice – this relates to the boundary spanning roles recommended by Galbraith. In addition, regular team meetings and a formal, gated project management process were considered best practices, reinforcing the need for strong lateral processes. Finally, early, bi-lateral communication was also mentioned in the form of early meetings, feedback between groups, and the team meetings. This points to the need for the integrative problem solving mode of communication.

Setting Project Direction

In order to determine which of the items found to focus on, an evaluation meeting was held. The areas of improvement were consolidated into 14 items based on the prior determination of “Try to Fix”. The team then evaluated the areas of opportunity to determine which were the most important, with each team representative rating the items. The team members considered impact to cycle time reduction, ease of correction, and the frequency each occurred when making their ratings. Below is the criteria matrix used to select the focus area.

Table 7: Focus Area Selection Criteria Matrix

1 = high priority, 4 = low priority

Category	Description	Assigned Priority				TOTAL
		LDC	DM	DMP	CV	
Process	Practicality of assay/tool from DA may not meet LDC's needs (\$\$, steps...)	1	1	1	1	4
Comm.	Problems encountered in LDC are not communicated to DA in a timely manner	1	1	1	2	5
Comm.	Ad-hoc communication between LDC & DA is inconsistent	1	1	1	2	5
Process	LDC is redoing some work	2	1	1	2	6
Scheduling	LDC schedules are not accurately forecast	1	2	1	2	6
Incentives	Screens are not always picked up by DA	1	1	4	1	7
Incentives	LDC's current metrics do not tie to project success	2	2	2	2	8
Incentives	DA priorities are not always in alignment with LDC (#/screens vs. #/D3's)	2	2	2	2	8
Team	LDC-Only meetings exclude DA for decision making and problem solving	3	1	2	2	8
Wait Time	Wait time between hand-off of assay/tools & start of work in LDC	2	2	2	2	8
Resources	Access to assay development/tools skills (CV)	2	3	2	2	9
Cycle Time	Tools Development/Production highest variability in work content & time	3	3	3	1	10
Resources	Access to small compound libraries	2	2	3	3	10
Cycle Time	Time to transition projects to LDC seems high	2	3	3	2	10

Based on the findings during these workshops, the team decided to work on improving communication and the process. The first four items in Table 7 are all linked directly to communication and the method of communication. The goal was to be able to better manage the transitions between groups and to educate the DAs on LDC processes and preferences. This links almost directly to the earlier literature about lateral processes and communication modes. Essentially, the gaps identified relate to the lateral processes currently in place that are not as robust as they could be. And, communication methods in the majority of completed projects studied ranged from Mode One: Serial Batch to

Mode Three: Early Involvement. Rarely did the LDC-DA team reach integrated problem solving and most communication occurred in Mode Two. Based on these findings, a new process was developed.

Chapter Five: Recommendations & Implementation

LFM Project Team Recommendations

There were three main recommendations made by the project team, which were:

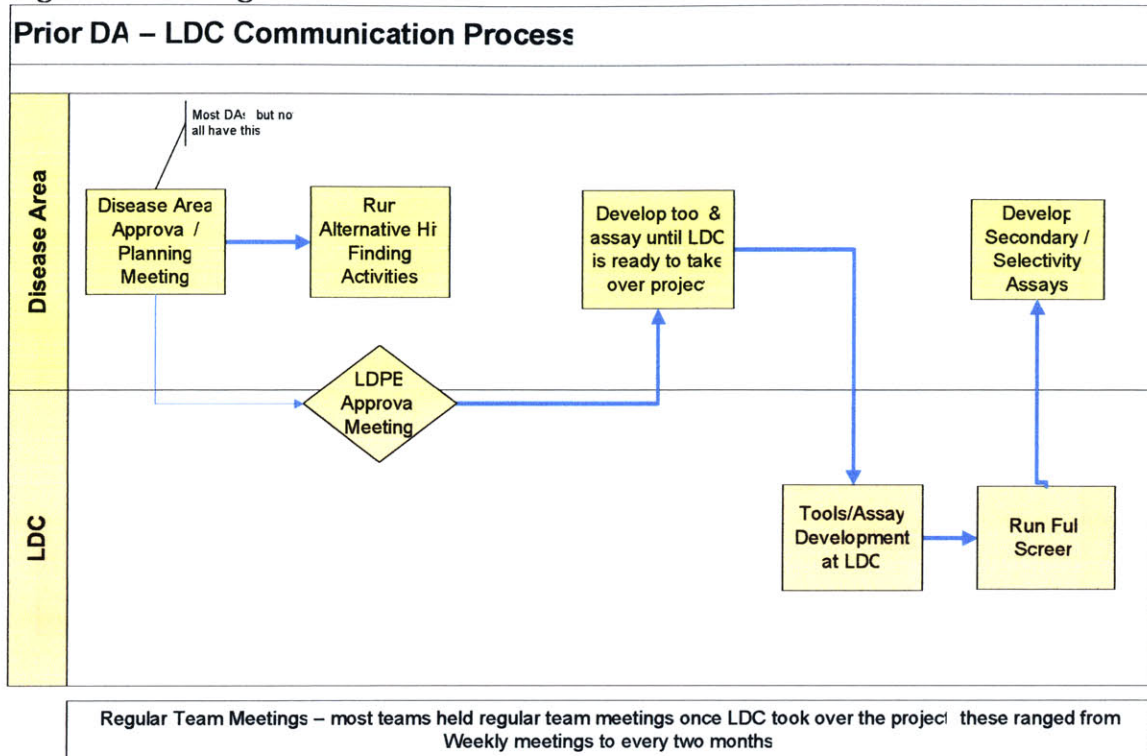
1. Facilitate effective communication between LDC and the DAs
2. Develop a standard method for managing work flow and roles and responsibilities between LDC and the DA
3. Educate the DA on HTS requirements and LDC preferences

By improving in these areas, projects should experience less rework between the DA and LDC and the wait time should be shortened as expectations are met. As documented in literature, it is important to eliminate the duplication of effort and to ensure that all tasks are accounted for during project planning³⁷. Because duplication of effort is a common occurrence in the current process, these recommendations attempt to reduce this.

Before going into more detail about the recommendations, below is an overview of the existing process. Most notable, LDPB happens earlier in the process and LDC will take over the project after LDPB either when the DA has provided an acceptable level of information or LDC has resources available. There is little integrative problem solving – generally work is done within the DA, then transferred to LDC when LDC is ready for the project.

³⁷ Jensen et al, 1998. Managerial Value in R&D. Drug Development Research 43:149-155.

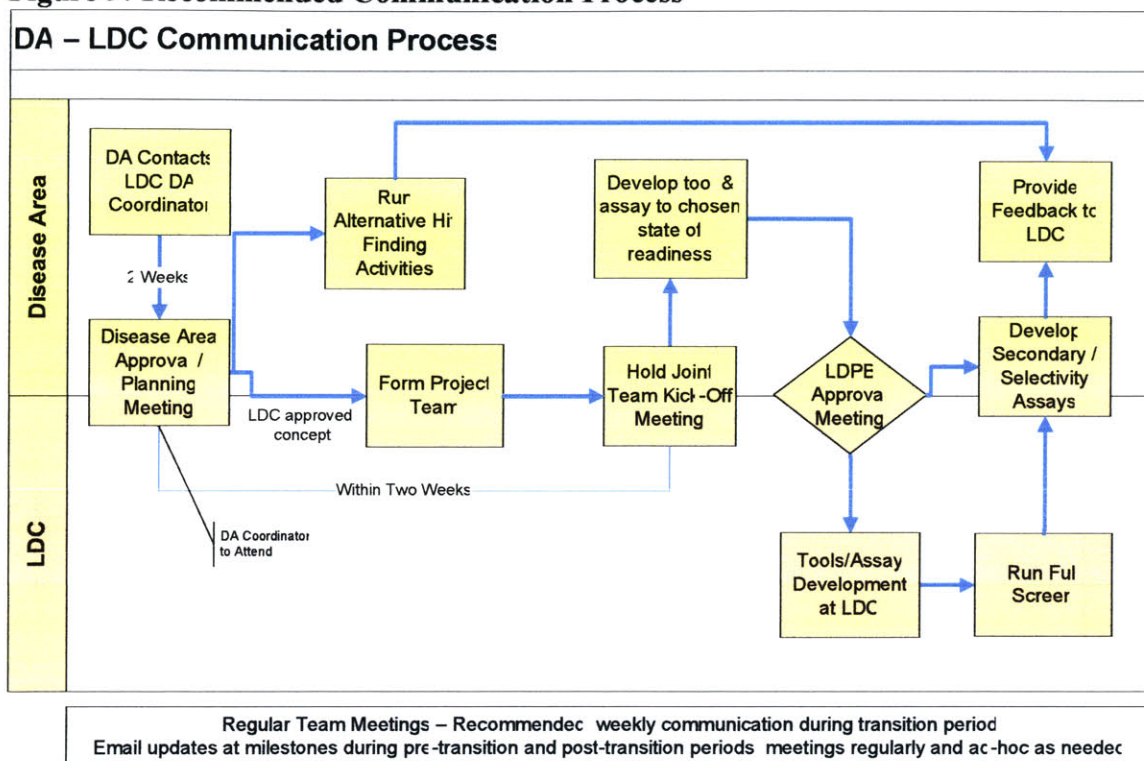
Figure 8: Existing Communication Process between DA and LDC



Facilitate Effective Communication & Standard Work Flow

The following process (see Figure 9) is recommended to enable effective communication throughout the project lifecycle and helps refine the existing lateral processes to enable better project management. The goal of this new process is to encourage the upstream – downstream communication to move consistently towards integrated problem solving through robust lateral processes. Essentially, the downstream organization (LDC) will be involved in the project at a much earlier stage and can help the DA in problem solving and planning. This will also enable LDC to plan for the project and perhaps begin work as needed to improve project cycle time.

Figure 9: Recommended Communication Process



All DAs should have a D1 Decision point; it is up to the DA to determine whether this will be a meeting and if a specific type of documentation is required. During this meeting, LDC will determine if the project is “concept ready” and will support the project through LDPB if it is concept ready. The LDC DA Coordinator should attend D1 Approval meetings in order to represent LDC and report back to LDC leadership on new projects.

Following the D1 Approval Meeting, LDC should assign a lab head to be the LDC representative on the project team. This responsibility may shift after LDPB. Generally, this will be the DA Coordinator unless another lab head is a technically better choice or the work allocation among DA Coordinators is uneven. This could also be a career development opportunity for associates interested in taking on some of this responsibility. If questions arise outside of the lab head’s area of expertise, they will either facilitate getting it answered with another person; or, if the project needs both protein and assay development support, two lab heads may be assigned to provide support.

Within two weeks of the DA D1 approval, a joint-team kick off meeting will be held (to be scheduled by the DA Project Manager). See the “Kickoff Meeting Agenda” (Appendix E) for details. LDC will be responsible for coming to the kick-off meeting with available resources and the timing of when the next several associates will become available as well as the number of other projects in the queue. The DA should also know their capabilities and resource availability, as well as which tasks have already been completed.

Work will be completed within the DA until the transition to LDC, with LDC providing help as needed. The DA will update LDC as each milestone is reached (or no less than monthly) and LDC will update the DA on resource availability and potential transition dates no less than monthly.

Once the DA has completed its work, they will present at the LDPB meeting. And, following LDPB, the project work will be owned by LDC and the DA will transition the project to LDC. During the transition, the project team should communicate weekly to review changes. If needed, associates can visit each other’s labs to work through transition issues.

Communication throughout the process will include regular meetings (Appendix F), ad-hoc meetings and email/phone calls/etc. Regular team meetings will be held no less than monthly throughout the process (the DA project manager is responsible for scheduling these meetings); in addition, regular updates will occur as milestones are reached in each group and ad-hoc communication will occur as needed. Real-time updates should be provided between groups for issues, schedule changes, decisions made, etc.

Throughout the process, a checklist (Appendix G) will be used to assess the readiness of the tool/assay for HTS. This checklist includes the tasks to be completed during the process and keeps track of who is responsible and accountable for each task. The work

will be divided at the project team kick-off meeting and could be reallocated during the project as resource availability and circumstances change.

Data will be kept track of in a project data sheet. This will include items such as protocols, materials, costs, experiment data, etc. This document will be owned by the DA until LDPB approval, at which point ownership will transfer to LDC. Both groups will have access to the document at all times. Following the screen, LDC will transfer the data to the DA. The DA should update LDC on the progress of the project no less than monthly until D2b has officially started or the project is terminated.

Role of the LDC DA Coordinator

Central to the communication process is the LDC DA Coordinator. Each DA in NIBR has a central point-of-contact in LDC, referred to as the “DA Coordinator” (this position currently exists). The role of the DA Coordinator will expand with these recommendations and should help facilitate better communication. If the workload for a particular DA is substantial, the DA Coordinator may delegate some responsibility to others in the organization. If the DA has any questions about who to contact in LDC, the DA Coordinator serves as the first person to contact. Below are the responsibilities of the DA Coordinator:

1. Work with the DA no less than 2 weeks prior to the DA D1 Approval meetings to review the projects that will be presented that month. Prior to the meeting, raise any questions with the project manager in the DA to ensure the project meets LDC requirements before the D1 Approval Meeting. The DA is responsible for contacting the DA Coordinator to begin this communication.
2. Attend DA D1 Approval Meetings, and provide input as needed from LDC. Following the meetings, communicate with LDC at the weekly phase review meetings which new projects were approved in the DA.
3. Attend each project kick-off meeting for their DA. Come to the meeting prepared with which LDC resources will be available when and how many other projects are in queue. The DA Coordinator needs to be able to provide estimates of when

resources will be available for their project. The responsibility for working on a specific project can be delegated to another person in LDC for scientific, capacity, or career development reasons.

4. Attend project team meetings until the project is transitioned to another lab in LDC. (Unless the project stays in the DA Coordinator's lab, then continue attending team meetings.)
5. Provide guidance to the DAs when they have questions about LDC, running a screen, developing protein/cells and assays, etc. If necessary, refer their questions to another person who is better able to provide a response.
6. Keep up-to-date on LDC resource availability and provide the DA with approximate dates that LDC will be able to begin working on their project. Update the DA as any changes to the schedule occur, or no less than monthly.
7. Help the DA prepare their LDPB presentation and provide support at the LDPB Meeting.
8. Following LDPB approval, work with the assigned lab and the DA to ensure a smooth transition of the project to LDC. Hand-off the communication for that project to the LDC lab assigned to the project.
 - a. Attend the first team meeting following transition with the new lab head and associates.
 - b. Walk the new team through the checklist, science, decisions made to date, and other relevant information at a team transition meeting.
9. Provide career development opportunities to LDC associates by delegating activities and projects to them as the associate requests them. Work with the associate to ensure that they are comfortable advising the DA and are knowledgeable on LDC resource availability.

Galbraith has recommended the use of coordinators in facilitating cross-organizational communication. These types of roles can be very effective in managing information flow and monitoring activities to encourage proactive responses to other group's plans. As is more typical in knowledge-intensive organizations such as NIBR, the coordinator also has control and significant influence over resource allocation. If the people in this role

effectively perform their duties, it can offset the need for a matrix structure (which can be complicated and should be used sparingly).³⁸

Galbraith also addresses the importance of identifying the people for these positions. NIBR is in a situation where these are the lab heads and the people are already chosen for the role. However, if they find that individuals do not possess the needed skills sets, NIBR may need to reassess how this is handled. For example, perhaps one or two people can take on this role as a full time position and handle all of the Disease Areas. The traits that Galbraith identified as critical to the success of the individual are:

- Possess the ability to influence without formal authority
 - Thrive in environments with high ambiguity
 - Comfortable with leveraging other's resources without having their own
- In addition, these people should report to a senior leader in the organization and should have access to any information needed to influence others.³⁹

Education of the DA

Partially because the Cambridge site is only 3 years old, many of the employees are unfamiliar with LDC and running screens. In order to bring new employees up-to-speed, LDC will embark on an effort to educate the DA. There will be two main facets to this: the DA Coordinator will own face-to-face training and there will be an on-line training document that everyone in NIBR can access. The training document will include items such as preferred vendors/materials, the communication process, screening technologies, and a general overview of the entire tools, assay, and screening process.

The DA Coordinator will also work with each new project lead to provide an overview of LDC and give them guidance on running a screen. If requested, they have material they can present to the DA as a large group and they will also be available for questions.

³⁸ Galbraith, et. al. pp. 166, 172.

³⁹ Galbraith, et. al. pp. 168 – 169.

Implementation

At the conclusion of the internship, the process was being piloted. Throughout the pilot, the project team will reevaluate the process and make any adjustments. Then, LDC leadership will be responsible for implementing this process in Cambridge. If successful, Basel will also implement the process.

The biggest potential problem identified with implementation is the increase in workload on the DA Coordinator. Currently, lab heads spend approximately 10% of their time on DA Coordinator activities. This workload will increase, and the group needs to be able to handle the extra responsibilities. The job has been scoped out, and the LDC leadership team is aware that the increased work load could cause problems in lab heads completing all of their duties. It should be noted that the increase in total workload should be short-term, because once the process is stable, there will be less work during the latter part of the process.

Following a successful pilot, the team will make any adjustments necessary. LDC leadership, with representation from the DAs, will present the new process to each DA in Cambridge. After the presentation, the DA Coordinators will work individually with the project teams to execute the implementation. The team will use continuous improvement and update the process as needed.

After the process has successfully been rolled out in Cambridge, the team will present the new process and results to Basel. One DA is located in both Basel and Cambridge and can help with the transition. The Cambridge and Basel LDC leadership teams will work to implement the new process in Basel.

Preliminary Results

Based on what occurred during the beginning of the pilot, the new process seems to be positively impacting cycle time. The pilot team met for the first kick off meeting to discuss the research project. The team includes representatives from both LDC and the

DA, and was the first meeting held with both groups together. The project had been approved by the DA, but had not yet been to LDPB.

During the kick-off meeting, the team worked together to determine which type of screen to run (cell based or biochemical) and what would be the best way to proceed for a difficult target. If this discussion had not been held, the DA would have made these decisions independent of LDC. Then, when the DA brought the project to LDPB, LDC may have repeated tasks the DA did or may have chosen to take the project in a different direction, causing delays due to rework. However, because the project team discussed this at an early stage, this rework should be prevented. It is difficult to determine how much time this will save due to the lack of data available, but it should be significant. This is an example of the team utilizing integrated problem solving rather than another mode of communication.

The pilot team also made their first change to the original process, recommending that the kick-off meeting be held as two separate meetings. The original recommendation was to meet to discuss the checklist and a brief overview of the science. The team determined that more time needed to be spent on the science, reconvening one week later to discuss the checklist and schedule.

The pilot team was well equipped to complete the evaluation of the recommendations and to implement the process across the organization. If LDC can maintain the discipline to implement the process and develop this communication into standard process, they should be able to reduce cycle time and better manage the cycle time variability.

Following this initial meeting, the pilot team has held several additional meetings and by all accounts, the process is working well. LDC has also begun to utilize this process with new projects. The biggest challenge in working with DAs that aren't familiar with the process is that these DAs tend to assume that LDC will now be performing more work. LDC management and the DA Coordinators have worked with these DAs to ensure they

understand that the early meetings are about communication and planning and do not automatically change the workload.

In addition, the organization has restructured since the completion of the project. LDC is working with their new leaders to determine how to manage communication in the new organizational structure. They are currently adapting the process to work in the new structure and are using these recommendations when planning how to run future operations.

Expected Impact

Based on the preliminary results and a qualitative analysis of the recommendations, Novartis will most likely see benefits from this project that will result in reduced cycle time, increased quality, and a neutral impact on costs.

Cycle Time

The main goal of this project was to reduce cycle time. During the process investigation, it was found that there is a fair amount of both wait time and rework. Both of these are typical areas of waste and were the two main areas that the project team wanted to improve.

If successfully implemented, NIBR should be able to reduce the rework through better communication. The main reason the team experiences rework is because the work is being performed in two groups; if the groups do not communicate effectively the project may incur rework. Either the first group will incorrectly perform work or the second group will needlessly repeat tasks because they don't know what was already done. This communication will take more time at the beginning of the project, but should more than pay back in reduced rework. There was not enough data to determine exactly how much cycle time results from rework, but anecdotally it seems to be noteworthy.

In addition, wait time exists between LDPB and the start of work in LDC. This seems to result from either the LDC requiring more information from the DA prior to starting work or LDC lacking resources to immediately begin projects. Through better

communication, the lack of information should be solved nearly completely. LDC should also be better equipped to plan their resources because they will have much earlier knowledge of demand. Similar to supply chain theories, the more advance notice a group has of customer demand, the better the group can plan their resources. This could include adjusting headcount in LDC or simply allocating work between the DA and LDC appropriately to maximize utilization of LDC and DA resources. The impact of this will be to eliminate some wait time, transfer some of the wait time to value-add work time, and some of the wait time will remain. It will be nearly impossible to eliminate wait time because even with better information, there will still be considerable variability in the process that will prevent seamless resource planning.

Quality

Quality was not a central focus of this investigation, but is still very important to NIBR. There are many potential definitions of quality, especially in the drug discovery realm, but for the purposes of this paper, quality results from making a more scientifically accurate decision about a project. One of the main outcomes of D2a is a list of compounds to pursue as a potential drug. If quality improves, these compounds will be better selected to enable a higher possibility of resulting in a drug. In order to better select compounds, the quality of the assay and target has a strong impact. With a better test, the compounds selected have the best chance of becoming a drug.

These recommendations will enable more minds to work on a project. By combining the subject expertise of the DA with the technical knowledge of LDC, each screen should produce higher quality results. This was evident during the first kick-off meeting held. The team discussed possible screening technologies and considered more options than what would have been evaluated with the DA alone working on the project. Because of these additional options, each project may end up with a better screen and therefore higher quality hits.

Costs

It is expected that these recommendations will be cost neutral. There is zero hard cost increase or decrease expected from increased communication. No capital purchases will

need to be made, resource requirements are not expected to increase; however, there is also no anticipated decline in costs. These recommendations also do not address material expenses (a high proportion of the costs) and it is expected those will not change.

There will be additional workload on the DA Coordinators during the implementation of this project. Following implementation, the workload should even out as the upfront time results in reduced time later in each research project. This cost during implementation is offset because there is a seasonal lull in demand for LDC and the DA Coordinators have more time than they normally would.

There is a possibility that the cost per screen could increase if increased quality requires increased costs. However, it is assumed that any increased cost that results in higher quality is in accordance with NIBR's strategy and will eventually pay back.

Based on knowledge of how the organization currently works, I also assume that even if there is an opportunity to reduce costs, NIBR will choose to instead do more with the same amount of money rather than reduce costs. NIBR will spend the same amount of money – either on more screens or doing more during each screen.

Additional Recommendations

In addition to the recommendations that the project team developed, there are several broader recommendations that I generated during my time at NIBR. These are:

1. Implement more control around the process
2. Expand on efforts to develop networks
3. Work towards shifting culture to mirror the highest level of lean manufacturing – continuous improvement and respect for people

Operations Management

I noted during my time at NIBR that the operations control and management are fairly lenient. For example, it is standard for NIBR employees at all levels to place orders for materials below a certain dollar amount without requiring further approval. In fact, it is

often easier for employees to order new material rather than locating and using excess material. Another example is management of timelines and tracking of cycle time data. One of the challenges of this project was the lack of data around cycle time. The source of data was a GANTT chart kept by LDC tracking each project. This is tracked at a fairly high level and the sample size is quite small (n~30). During meetings where project timelines and resources are discussed, reasons for delays or changes to the schedule were not kept track of nor were they scrutinized. There does not seem to be much penalty placed on projects that finish late, nor are the reasons for delays analyzed to look for opportunities for improvement. At least within LDC, more operations management control could help the organization improve costs and forecast accuracy.

I recommend that LDC do several things to begin to control their process. The first is to track schedule changes, including the reason for the change. Then, these data can be used to determine what issues commonly occur and how to prevent these from happening. This can also help LDC increase their forecast accuracy by presenting realistic expectations of how long certain tasks take to complete. There was a resounding preference from the DA's that an accurate cycle time forecast was more important than the actual length of time. This is supported by psychological literature that suggests that people are less dissatisfied waiting if they know how long the wait will be.

In addition, I recommend that LDC implement standard group level metrics, such as average cycle time, labor hours spent per project, the amount of overtime employees are working, etc. They collect very basic metrics, the number of projects completed, but do not go into more depth. This can help in many ways; one such way is improving employee satisfaction. The amount of overtime per employee, and also the amount of "odd hours" (nights and weekends) employees are working, is very important for employee satisfaction. It is fairly common for LDC associates to work long/odd hours during screening and they have expressed dissatisfaction with this. By tracking this information, LDC could quantify the impact and perhaps begin to work out a way to change this.

Developing Networks

Because NIBR in Cambridge is a fairly new organization and has hired people quite rapidly over the last several years, networks are not necessarily as developed as they could be. There were a few methods recommended by Galbraith that NIBR is not currently utilizing: rotational assignment, co-locating, and communities of practice.

NIBR does have internal hiring and encourages people to move between positions, however there aren't many options for formal rotational assignments. This could be especially effective at the associate level. For example, an associate could move from LDC to a Disease Area, and then come back to LDC perhaps as a lab head or higher-level position. This would provide the associate with additional learning and would also help both organizations learn about each other.

NIBR is spread between two main locations in two different countries, Cambridge and Basel, Switzerland, resulting in difficulties if project teams stretch across the oceans. The structure between the locations has most DA's centered in one location with the support groups and platforms duplicated in both locations. For example, LDC has full capabilities in both locations. There is some potential for duplication of effort and equipment, but in order to manage with the current structure LDC should try to assign projects based on location. They do currently try to do this, with about 80% of projects assigned to the local LDC team. This should be continued, and recognized as a key component to future success.

Finally, NIBR could develop communities of practice in its organization. Some of these are informally in existence, for example with NIBR intramural sports teams. Communities of practice are organizations focused on a particular topic that allows employees to learn about other areas as well as meet people with similar interests. These can be related to science or not. NIBR could form these groups and encourage participation in them. One example of a non-science group that many companies have is minority-focused organizations, such as a women's group. NIBR could formalize these

by finding leaders in the organization to start such groups and provide funding to the groups.

Lean Manufacturing

Novartis, A.G., has a six-sigma/lean-manufacturing practice and associated courses. However, these are mainly in other areas of the company and have not penetrated into NIBR. Because of NIBR's focus on novel research, I don't recommend a concentration on lean manufacturing. However, the basic principles of lean, continuous improvement and respect for others, could be very successfully utilized. Continuous improvement is instilling a focus on improving processes into the culture of the organization. This would mean that people within the organization are empowered to make changes to improve the workflow, with the intended impact of improving cost, quality, and/or time. Respect for others is exactly what it sounds like, considering all employees (as well as suppliers, customers, contractors, etc.) when making changes or decisions. NIBR already has decent respect for others in its culture, but could perhaps improve this respect of the associate, non-PhD, population. In general, with a bit more attention to lean manufacturing principles, NIBR could begin to realize additional benefits from their scale without sacrificing the product development expertise.

Chapter Six: Hypothesis Investigation

At this point, I'd like to revisit the proposed hypothesis to determine if any of the findings are consistent or inconsistent with they hypothesis. The primary hypothesis was that NIBR is not managing its product development process in accordance with widely accepted literature and that this is ultimately causing delays and problems in the development cycle. In addition, NIBR has not adopted these practices as a result of the relatively small amount of time the Cambridge site has existed as well as the very strong focus on product development.

The cycle time data provided the initial evidence that there were issues with the processes used when transferring projects from the DA to LDC. Wait times in processes are generally red flags that something is wrong with the process. And, a wait time as long and with as much variability as the one from LDPB to D1 (13 weeks average, 12.5 weeks standard deviation), signals a particularly large problem. Further investigation linked this delay to a lack of communication between LDC and the DA. This investigation also pointed out another impact of the communication process – the tendency for LDC to repeat work that the DA had performed.

When reviewing the product development literature, strong ties were made between communication methods, lateral processes, and the effectiveness of product development projects. The literature suggests that effective product development processes between upstream and downstream organizations utilizes bi-lateral, early, and frequent communication results in better cycle time and higher quality products. Integrated problem solving was a communication method rarely seen in the transition from the DA to LDC (in fact, just wording this process as a “transition” implies a lack of integration between the two groups). Due to this, it does appear that NIBR is experiencing cycle time and quality delays due to both its communication methods. In addition, the literature points to the importance of lateral processes as one of the pillars of effective product development organizations. At NIBR, the only formal process in place was the LDPB meeting. This can be safely assumed to be inadequate given the complexity of

their product development. By deliberately structuring and guiding their lateral processes, NIBR will be able to see the benefits of this pillar.

The combination of evidence collected with at NIBR as well as the information from literature, suggests the initial hypothesis is true. Now, let's examine the reason why NIBR has failed to implement these recommendations.

NIBR has existed within Novartis in some manner for quite a long time. However, the organization in Cambridge had been formed three years prior to this investigation. The two main objectives of the site were to ramp up quickly and to simultaneously develop new drugs. These two factors left little time to devote to process implementation and improvement, and many processes developed as the organization formed. In addition, formal and informal networks reflect the maturity of the organization. Networks take time to develop, and NIBR has not had much time to develop these networks. Networks represent another pillar of organizational structure; and one that NIBR has not fully developed. I did not focus on this during the project, mainly because I think these will develop over time and NIBR is doing a good job of holding events and encouraging people to meet each other.

A Case Study – Hewlett Packard⁴⁰

In order to tackle the last portion of the hypothesis, I'd like to reference a study performed at one of Hewlett Packard's sites in the early 1990's. This division of HP was focused primarily on developing the most technically advanced products, with manufacturing and processes in place mainly to support product development. The findings of this study showed that HP was failing to capitalize on process improvement efforts due to two primary reasons: first, the belief that products were the source of virtually all economic returns; and, second, difficulty in estimating the benefits of process improvement projects resulting from a lack of good quality economic data that could be related to process improvements and a local, rather than global, focused approach to process improvement.

⁴⁰ Henderson, et. al. A study was conducted at one HP site by five MIT Leaders for Manufacturing Students spanning from 1989 – 1991. The cumulative results of these theses were consolidated into this paper, led by MIT Faculty Member Rebecca Henderson.

In addition, this study examines the fact that HP most likely experienced these difficulties as a direct result of their historical success. The division had been successful due to its relentless focus on developing the best products, which seemed to lead to the lack of process development. HP was able to develop excellent products due not only to their technology and outstandingly committed and fluid organization; there was also a network of formal and informal mechanisms that supported and reinforced that product design was the primary sources of value for the division. The question then arose that if the division moved to a more process focus organization, would their product development skills wane? Five years after these studies were conducted, HP has been able to improve its throughput threefold through a stronger focus on process development.

This example with HP fairly closely parallels NIBR. Although NIBR has the additional complication of being a new organization, it is also a division strongly focused on product development. In fact, NIBR could be viewed as the extreme example of what HP was experiencing. NIBR almost solely employs product focused people. LDC does have a Technical Operations department that includes one mechanical engineer, but this department focuses entirely on the physical space and on installing and maintaining lab automation, equipment, and instruments. They do not focus on improving process; mainly because they do not have the time to do so (their time while I was on site was spent mainly fire-fighting and installing new equipment). From this perspective, it can be said that NIBR doesn't really have anyone focused on process improvement. Like HP, this could also be due to the overwhelming focus on product development and the belief that products are where the money lies.

The HP example helps illustrate the impact that being focused on products can have on process development and improvement and closely parallels what NIBR has experienced. This, along with two others, was the first time NIBR in Cambridge tasked someone with looking exclusively at process. Like HP, NIBR could also improve its operations with some attention given to processes. By continuing to do so, NIBR could improve cycle time, quality, and costs.

Chapter Seven: Conclusion & Summary

In conclusion, NIBR is a classic example of an organization focused on exploration attempting to implement some benefits of coordination. By structuring their organization mainly around products, with a cross-section of support functions, NIBR has worked to maximize their ability to develop novel drugs. However, the interaction with at least one of these support functions can be improved by implementing basic communication and process improvements.

By focusing on improving lateral processes to enable more integrated problem solving between the upstream and downstream organizations, NIBR can realize some advantages of coordination without sacrificing their exploration abilities. The recommendations outlined in this thesis serve the primary goal of formalizing the communication process to consistently enable project teams to move to the latter modes of communication and work together to achieve their goals. Based on the initial results of the pilot, this process was effective in creating an integrative problem solving mode for the project teams participating in the pilot. The team shifted to this mode by utilizing the lateral process recommended and adding some structure to their communication.

After LDC and the Disease Areas have implemented this more robust process, the organization can move towards further process improvement. This new process should create the baseline for better information sharing and learning across organizations and present the opportunity for more process improvement. In addition to the immediate benefits of cycle time reduction and quality improvement, the organization will be able to better capitalize on future improvement opportunities.

Finally, I'd like to again thank Novartis for their great support, especially the people who directly supported me on my project team. Without the openness and reception I received at NIBR, I would not have been able to accomplish my project goals. This was a great experience for me, both as a leader and as an opportunity to learn about the pharmaceutical industry. Thanks again to everyone who assisted me!

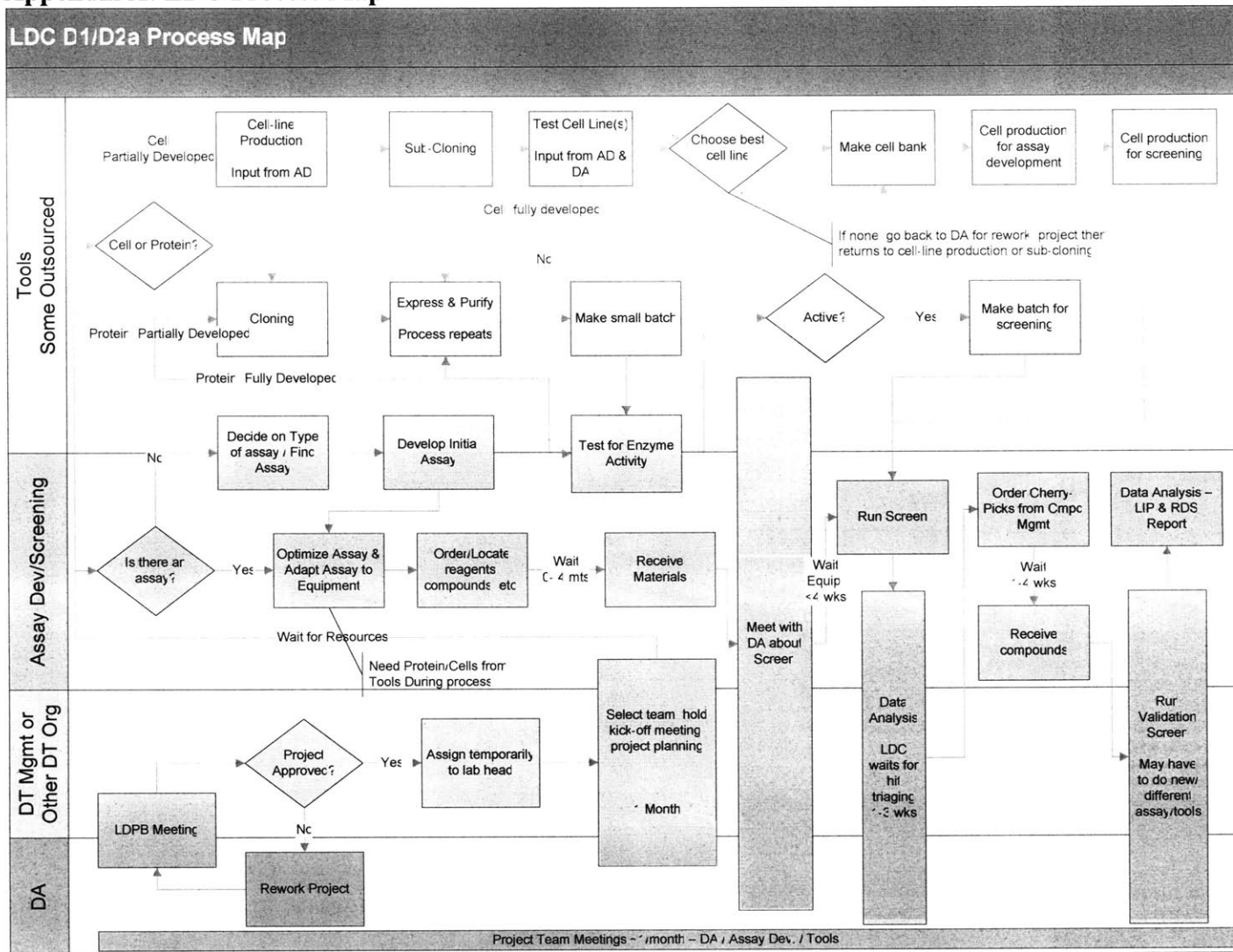
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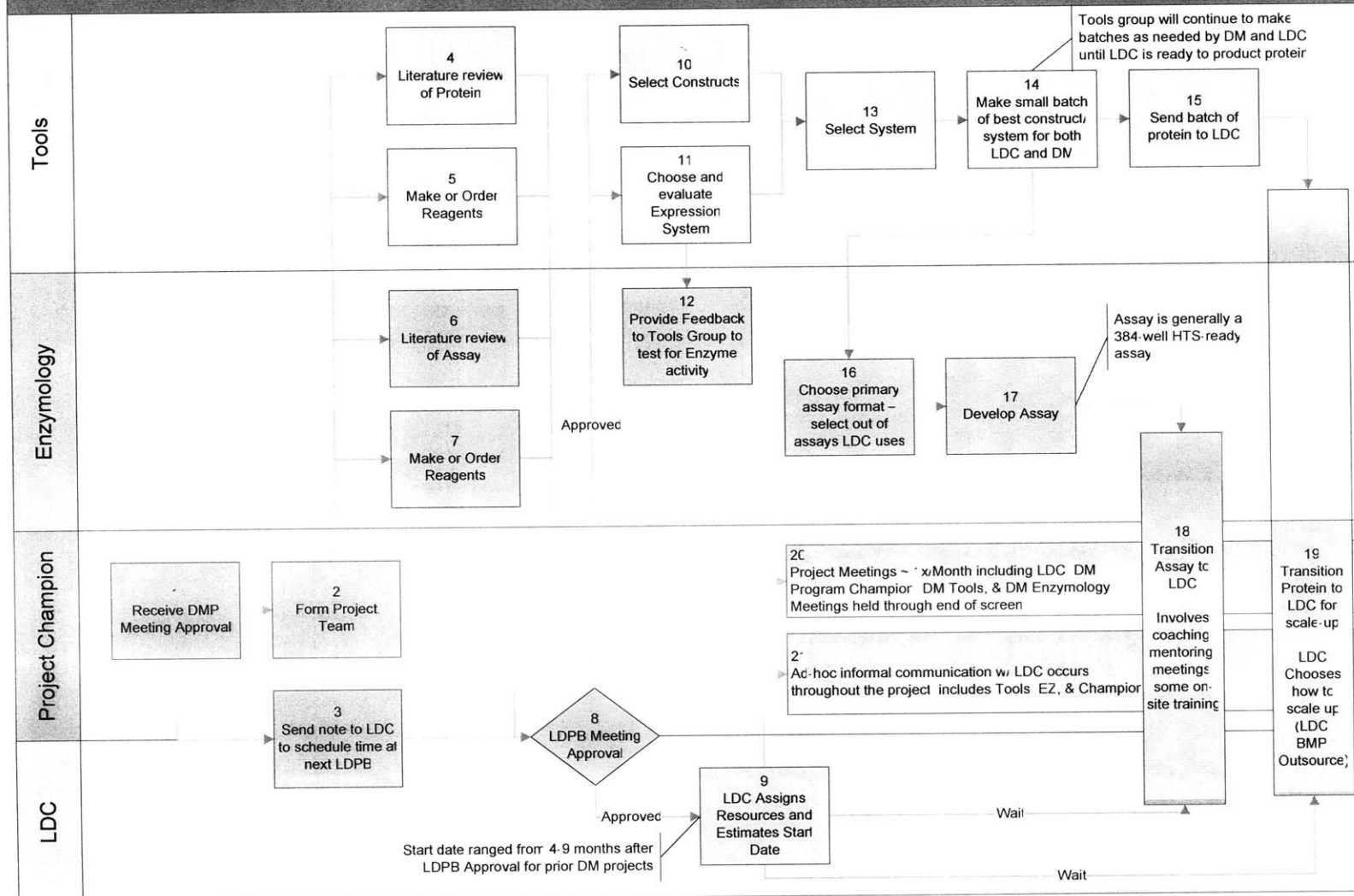
Appendix

Appendix A: LDC Process Map

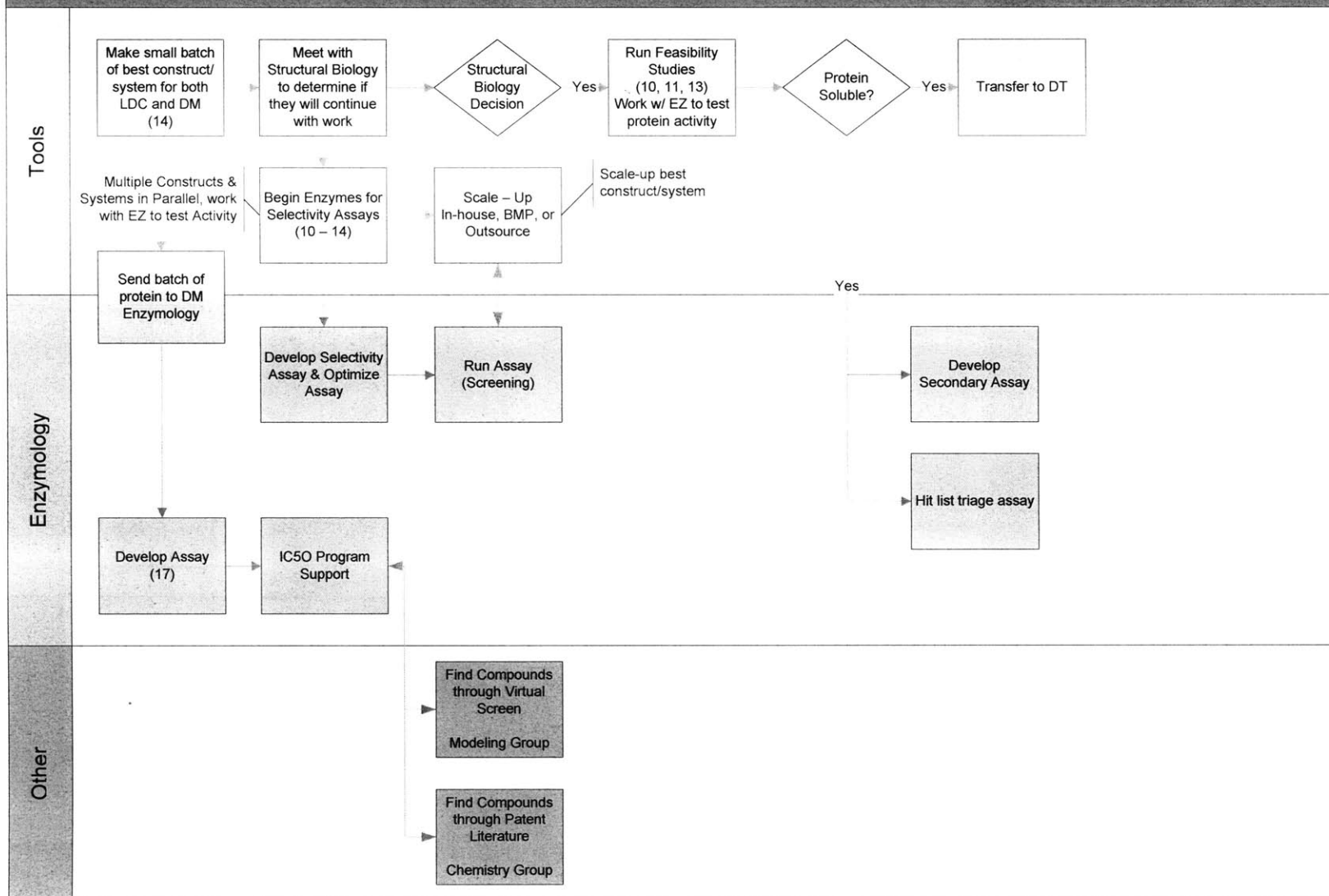


Appendix B: Diabetes & Metabolism Process Maps

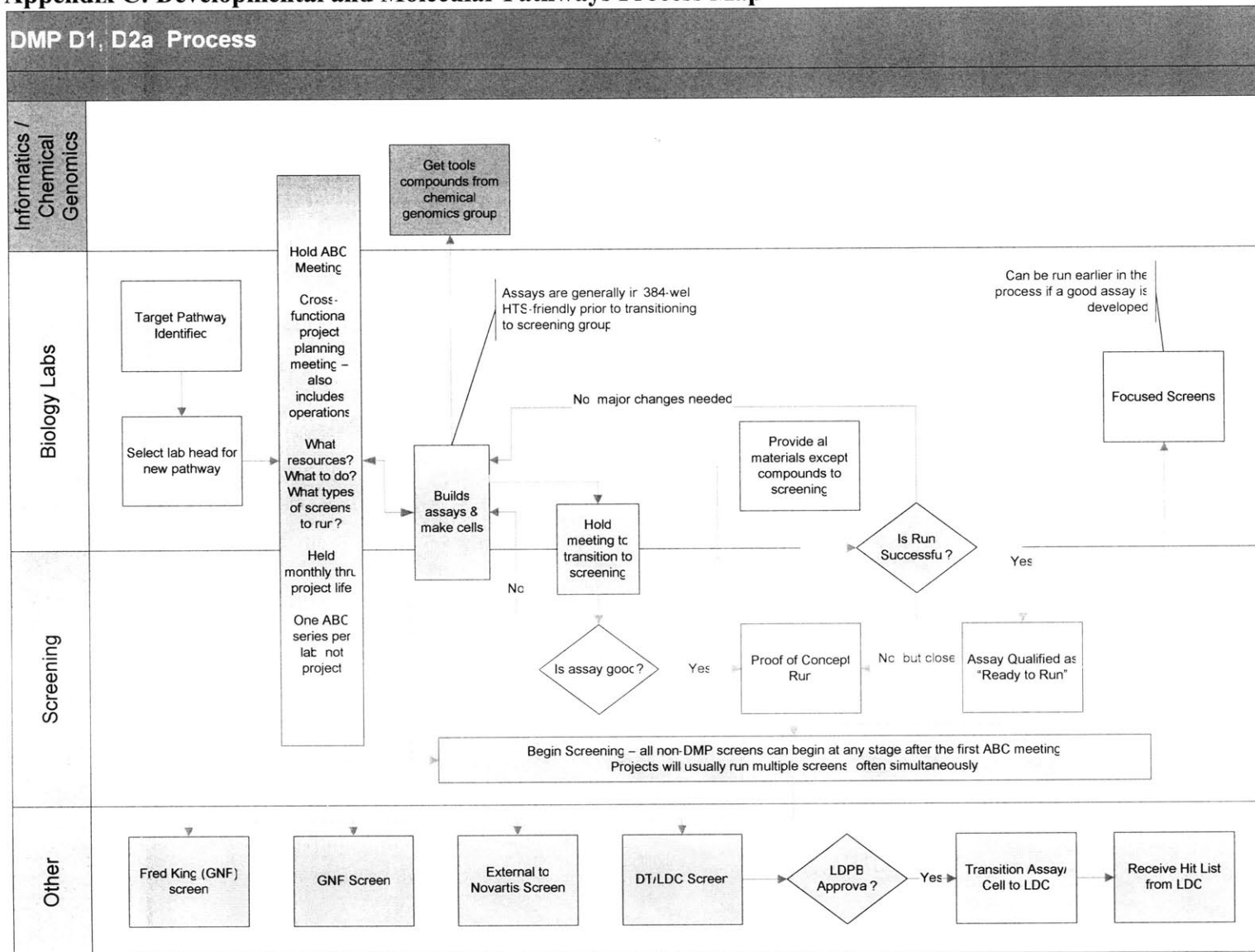
Diabetes & Metabolism Process Map – D1 through Transition to LDC



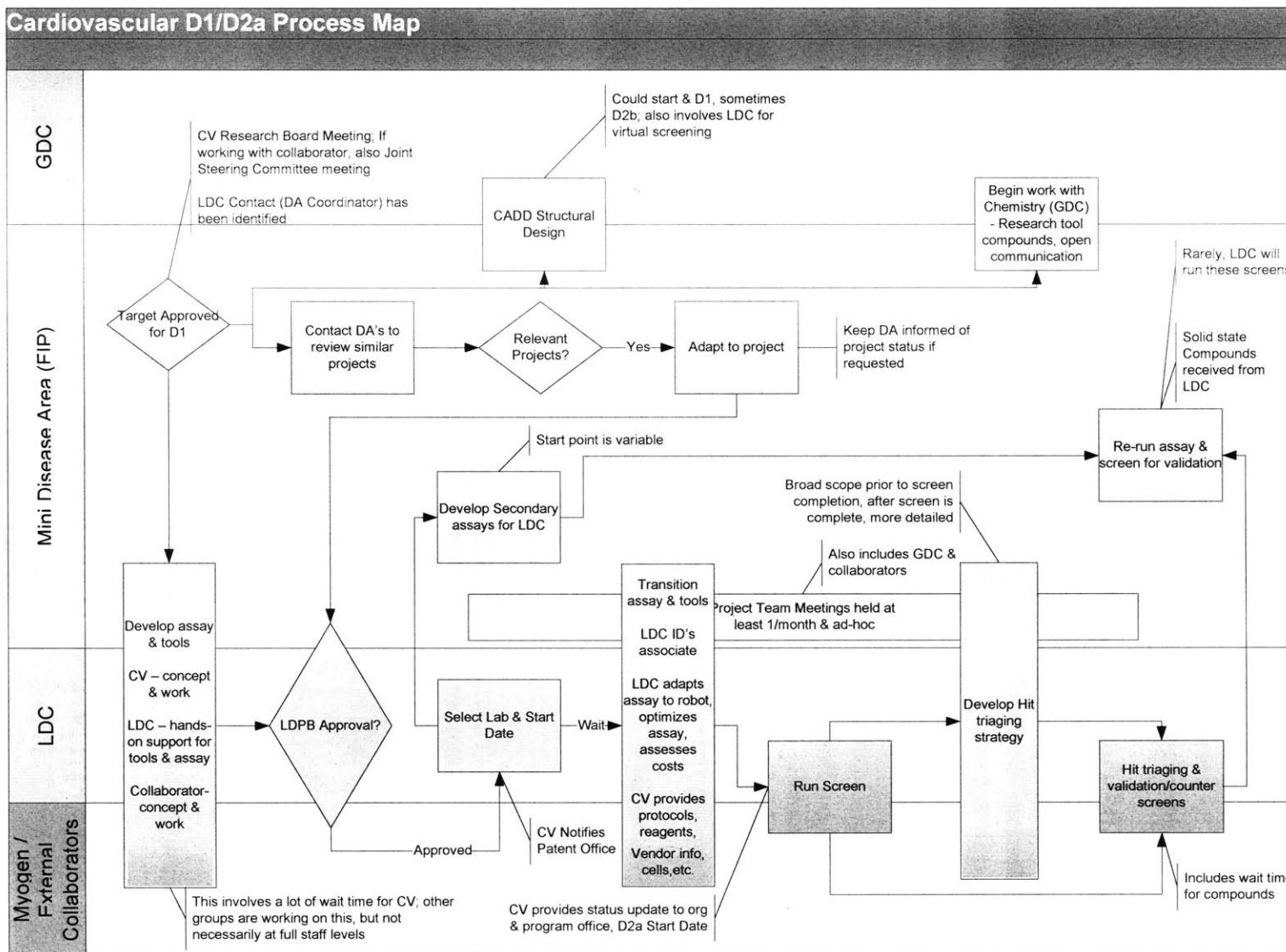
Diabetes & Metabolism – Activities Post-Transition to LDC



Appendix C: Developmental and Molecular Pathways Process Map



Appendix D: Cardiovascular Process Map



Appendix E: Kick-off Meeting Agenda

D1 DA-LDC Joint Team Kick-Off Meeting – Part One of Two

Attendees: DA – Project Manager, Lab Head, Associates
LDC – DA Coordinator, Other Interested Parties

Timing: 1 - 2 weeks after DA Approval of D1 Transition
Meeting time estimated ~1 Hour

Facilitators: DA Project Manager
Scheduled by DA Project Manager

Goal of Meeting: To share information about the project and to make preliminary science decisions (cell vs. biochemical, number of assays, etc.)

Agenda:

1. Review DA Approval Meeting slides, including biology of the target (if needed)
2. Fill out Project Data Sheet – DA to have completed what they know (may be minimal)
3. Set the direction for D1/D2a and determine what the work will be required (antibody production, cell based screen(s), biochemical screen(s), mass spec screen, number of protein variations, etc.)
4. Q&A
5. Schedule next meeting time

Pework:

1. **DA**
 - a. Fill out Project Data Sheet
 - b. Send project slides to the LDC project team
 - c. If possible, update checklist with more specific tasks
 - d. Set Project Team
 - e. Perform literature search on target & send literature to LDC
2. **LDC**
 - a. Review DA Documentation
 - b. Determine LDC resource availability
 - c. Determine if both tools & CSO should be present at meeting

Post Meeting Action:

1. DA – update state-of-readiness checklist with specific tasks based on outcome of meeting (LDC to assist)

D1 DA-LDC Joint Team Kick-Off Meeting – Part Two of Two

Attendees: DA – Project Manager, Lab Head, Associates
LDC – DA Coordinator, Other Interested Parties

Timing: Within 1 Week of First Meeting
Meeting time estimated ~1 Hour

Facilitators: DA Project Manager
Scheduled by DA Project Manager

Goal of Meeting: To determine roles & responsibilities and work through state-of-readiness checklist

Agenda:

1. Review Decisions made at last meeting; update science as needed
2. State-Of-Readiness Checklist
 - a. DA to update the status for what's been completed to date, including providing data on the project data sheet when appropriate
 - b. DA & LDC to work together to determine who will complete the remaining steps (some may be joint efforts)
 - i. DA prepared with what resources they will have available to complete each task, including timing of availability
 - ii. LDC prepared with what resources they will have available to complete each task, including timing of availability
 - c. Team to estimate how long it will take to complete DA items & set a tentative date (maybe a date range) for transfer to LDC
3. Q&A
4. Schedule next meeting time

Pework:

1. **DA**
 - a. Update Status for Items Completed/In-Progress on State-Of-Readiness checklist, send to LDC DA Coordinator
 - b. Update Checklist with specific tasks, send to LDC
 - d. Determine resource availability & capabilities for the tasks on checklist
2. **LDC**
 - a. Review State-of-Readiness checklist
 - b. Determine LDC resource availability

Appendix F: Team Project Meeting Agenda

Monthly/Milestone Project Meeting

Attendees: DA – Project Manager, Lab Head, Associates
LDC – DA Coordinator/Lab Head, Associates

Timing: After each milestone is reached or monthly, whichever is sooner

Facilitator: DA Project Manager
Scheduled by DA Project Manager

Goal of Meeting: To update each other on the status of the project, review timelines and resources, and discuss any issues

Agenda:

1. Status Update
 - a. State-of-Readiness Checklist – review items that have been completed since the last meeting and where the project currently is in process
 - b. Review updates to project data sheet since the last meeting
2. Scheduling/Resource Planning
 - a. Review current schedule, make adjustments as needed
 - b. Both groups estimate when resources will be available and adjust state-of-readiness checklist responsibility if needed to ensure there is no wait time
3. Issues/Comments/Decision Making
 - a. Review any issues in process
 - b. Discuss upcoming decisions
 - c. Q&A
4. AOB

Pework:

1. Pre-Transition to LDC
 - a. DA
 - i. Update project data sheet
 - ii. Update status for checklist items (completed, in-progress, delayed, not started), for completed items replace the date with actual date completed
 - iii. Highlight any date changes
 - iv. Know what resource availability will be
 - v. Project Data Sheet Filled in – send to LDC at least 1 week prior to meeting
 - b. LDC
 - i. Update on resource availability, timeframe for transition to LDC
 - ii. Review Project Data Sheet and be prepared with questions/Suggestions
2. Post-Transition to LDC

- a. LDC
 - i. Update project data sheet
 - ii. Update status for checklist items (completed, in-progress, delayed, not started), for completed items replace the date with actual date completed
 - iii. Highlight any date changes
 - iv. Know what resource availability will be going forward, including equipment
 - v. Project Data Sheet Filled in – send to DA at least 1 week prior to meeting
- b. DA
 - i. Review Project Data Sheet and be prepared with questions/Suggestions
 - ii. Provide status update on secondary/selectivity assay development and other pre-D2b activities

Appendix F: State-Of-Readiness Checklist

EXPERIMENTAL OPTIMIZATION CHECKLIST

Criteria for biochemical assays:	Comment/Result	Status	Timeline/ Milestone	Responsibility	
				DA	LDC
Protein Prep					
Method					
Bacterial/Insect/Mammalian					
Media requirements (cat #'s, recipe)				<input type="checkbox"/>	<input type="checkbox"/>
Growth Conditions				<input type="checkbox"/>	<input type="checkbox"/>
Induction requirements (bac)				<input type="checkbox"/>	<input type="checkbox"/>
Virus Availability (insect)				<input type="checkbox"/>	<input type="checkbox"/>
Virus protein expression moi (insect)				<input type="checkbox"/>	<input type="checkbox"/>
Passage method (mamm)				<input type="checkbox"/>	<input type="checkbox"/>
Confluency considerations (mamm)				<input type="checkbox"/>	<input type="checkbox"/>
Expression					
DNA sequence				<input type="checkbox"/>	<input type="checkbox"/>
Vector Map				<input type="checkbox"/>	<input type="checkbox"/>
Proof of expression and solubility				<input type="checkbox"/>	<input type="checkbox"/>
Proof of activity				<input type="checkbox"/>	<input type="checkbox"/>
# of Constructs to test				<input type="checkbox"/>	<input type="checkbox"/>
Validation					
Estimate of mg/L yield-yield vs. total mg required(total culture volume <200L preferred)				<input type="checkbox"/>	<input type="checkbox"/>
Total mgs needed(enough for 1.2x10 ⁶ wells)				<input type="checkbox"/>	<input type="checkbox"/>
Analytical sizing					
Mass Spec-size, PTM					
Gel & Western analysis (Ab avail?)					
Stability					
Prolonged storage conditions (evaluate stability 1-3mos at -80)				<input type="checkbox"/>	<input type="checkbox"/>
Freeze/Thaw capabilities (once, twice, etc)				<input type="checkbox"/>	<input type="checkbox"/>
Storage buffers				<input type="checkbox"/>	<input type="checkbox"/>
Non-specific activity level					
Assay					
Signal linearity with protein concentration and time (30 minute minimum)				<input type="checkbox"/>	<input type="checkbox"/>
If protein is not pure or a membrane prep, is there non-specific/background activity?				<input type="checkbox"/>	<input type="checkbox"/>
Optimal substrate selection				<input type="checkbox"/>	<input type="checkbox"/>
Optimization					
Use LDC's DOE to determine conditions for further evaluation				<input type="checkbox"/>	<input type="checkbox"/>
Salt				<input type="checkbox"/>	<input type="checkbox"/>
Divalent cation requirement (Ca ²⁺ , Mg ²⁺ , Mn ²⁺)				<input type="checkbox"/>	<input type="checkbox"/>
Chelating agent (EDTA, EGTA)				<input type="checkbox"/>	<input type="checkbox"/>
Reducing agent (DTT, BME, glutathione)				<input type="checkbox"/>	<input type="checkbox"/>
Detergents				<input type="checkbox"/>	<input type="checkbox"/>
Carrier protein				<input type="checkbox"/>	<input type="checkbox"/>
Optimal buffer and pH				<input type="checkbox"/>	<input type="checkbox"/>
DMSO sensitivity (titration)(0.5% preferred)				<input type="checkbox"/>	<input type="checkbox"/>
Control/test/tool/reference compound IC ₅₀				<input type="checkbox"/>	<input type="checkbox"/>
K _M or K _D				<input type="checkbox"/>	<input type="checkbox"/>
Set substrate concentration ≤ K _M or K _D				<input type="checkbox"/>	<input type="checkbox"/>
<10% substrate/ligand consumption				<input type="checkbox"/>	<input type="checkbox"/>
Miniaturization & HTS Validation					
Minimize # of steps in assay				<input type="checkbox"/>	<input type="checkbox"/>
Miniaturization to 384 or 1536-well plate				<input type="checkbox"/>	<input type="checkbox"/>
Total length of assay < 2 day				<input type="checkbox"/>	<input type="checkbox"/>
Z' determination				<input type="checkbox"/>	<input type="checkbox"/>
Reagent stability					
Under assay conditions over 12-24 hours				<input type="checkbox"/>	<input type="checkbox"/>
Protein freeze/thaw capacity				<input type="checkbox"/>	<input type="checkbox"/>
Long-term storage capacity				<input type="checkbox"/>	<input type="checkbox"/>

EXPERIMENTAL OPTIMIZATION CHECKLIST

Criteria for cell-based assays:	Comment	Status	Timeline/ Milestone	Responsibility	
				DA	LDC
Cell Line Development					
Growth / Clonal Selection					
Media recipe (cat #'s, use of common reagents)					
Common Medium → DMEM, F12, RPMI, MEM					
Common Selective agents → G-418, Blasticidin, Hygromycin					
Passage # with signal stability (25-30 preferred)					
Suspension cells-Growth density/plating density ratio (>3:1 growth:plating preferred)					
Maximum confluency for adherent cells (>75% preferred)					
Doubling time					
<36hrs in order to run ~100 plates/day					
Signal recovery time after cryopreservation					
Cell line developed and signal verified					
Plate/plastic coating required?(Costar plastics preferred)					
Assay					
Cell density for plating (# cells/well)					
Incubation (time course)					
Reagent concentrations					
DMSO sensitivity (titration) (0.5% preferred)					
Control/test/tool/reference compound EC ₅₀					
Miniaturization & HTS Validation					
Format: Miniaturization to 384-, 1536-well plate					
Minimize # of steps in assay and cell preparation					
No need to centrifuge cells is preferred					
Total length of assay (including cell plating) < 3 days					
Plate uniformity, edge effect					
Z' determination					
Stability					
Reagent stability over assay length and temperature					