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Faculty of Business Economics

Master of Management

Master's thesis

Big in innovation: The importance of scale and scope in generating innovation (qualitative study)

John Gocke

Thesis presented in fulfillment of the requirements for the degree of Master of Management, specialization Strategy and Innovation Management

SUPERVISOR :

dr. Relinde COLEN

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Flexibility and Reliability

(The New Evolution in Pharmaceutical Development)

May 7,2021
Student: John Lance Gocke
Promoter: Linde Colen
For the MOM Program of the University of Hasselt

Abstract

This paper delves into the question of what organizational size is best equipped to innovate within the pharmaceutical field. The pharmaceutical field's complexity has increased the difficulty of applying insights from the size debate in innovation to the pharmaceutical field. This paper interviewed executives from pharmaceutical, biotech, and insurance backgrounds to understand a richer picture of the field. This research found that due to the complexity of the pharmaceutical development process, the factors that underlie our understanding of significant innovations are split. Small biotechs are able to achieve the novelty aspect efficiently, but are unable to bring the API (Active Pharmaceutical Ingredient) to commercialization because of high capital and purity requirements. So, the impact element of a disruptive innovation is observed in pharmaceutical companies who commercialize the innovation. This insight leads to an understanding of the pharmaceutical industry as an ecosystem where both biotech firms and pharmaceutical companies are necessary for optimal innovation.

Keywords: Innovation, pharmaceutical, biotech, disruptive

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Definition of Key Terms

API: Active Pharmaceutical Ingredient

Biotech company: refers to companies that utilize biotechnology. Within this paper, biotechs will be referring to emerging biotech companies in the pharmaceutical industry.

Biotechnology: The application of microbial, animal, or plant cells or enzymes to synthesize, break down, or transform materials (Smith, 1988, p.1). Biotechnology is a series of techniques for achieving various desired aims and less a focus on a series of products (Smith, 1988). Biotechnology encompasses a varied range of industries such as pharmaceuticals, agriculture, and even the energy sector (Gilsing et al, 2006; Wieczorak, 2003; Demirbas, 2019).

Disruptive Innovation: According to Christensen, disruptive innovation is a novel process or product that creates a disruption by appealing to an unserved or low end customer, eventually taking over the market (Christensen et al., 2015). Terms such as breakthrough, radical, disruptive, and discontinuous are often used interchangeably in management literature (Kovacs et al, 2019). They argue that these four terms vary along two dimensions - novelty and impact (Kovacs, Marullo, Verhoeven and Looy, 2019). This paper will focus on innovations with both high novelty and high impact.

Paragraph IV challenge:a company applies for FDA approval to market a generic drug based on a brand name drug before the patents related to a brand-name drug have expired (FDA, 2021).

Pharmaceutical is often used to refer to companies with over ten billion dollars in annual revenue (IQVIA, 2019). In this paper, pharmaceutical company refers to incumbent companies in the pharmaceutical industry. This includes incumbent biotech companies such as Genentech and Amgen.

Pharmaceutical Company: refers to a company that develops medicines to solve health issues in people.

Sustaining Innovation: An innovation that does not cause a disruption in the industry. This often is a small improvement on an existing product or service (Christensen et.al, 2015).

Introduction

Industrialization is a relatively recent development in human history. Beginning in Britain in the 18th century, factories began to develop where tasks could be subdivided and specialized to enhance productivity (Van Neuss, 2015). Joseph Schumpeter examined this change in his books *Theory of Economic Development* in 1911 and *Capitalism, Socialism, and Democracy* in 1942 as well as numerous articles that he wrote. Schumpeter, in his later work, found that there was a tension for companies as they grew larger between scale advantages and bureaucratic disadvantages. Based on Schumpeter's writing, these bureaucratic aspects of a company slow down the development of innovation and result in less interesting products. Since his 1942 book *Capitalism, Socialism, and Democracy* was published, there has been a persistent discussion in academia about whether innovation is hindered within large corporations. This is valuable because companies, and society in general, want to make the best use of limited resources for developing solutions to problems. If academia and the business community are unaware of advantages related to scale and how to handle the repercussions of increased bureaucracy, resources will be misallocated.

This paper looks at what factors determine the best size for a pharmaceutical company. This discussion on the optimal size for innovation is particularly important in the pharmaceutical industry because an innovation can result in life-saving medicines. The world would look very different if Alexander Fleming had not discovered penicillin or if Frederick Banting and Charles Best did not successfully isolate insulin (Bennett and Chung, 2001; Karamitsos, 2011). This paper serves as a contribution to the larger economic discussion of development optimization in comparison to size.

This thesis paper serves as an initial source of information for those interested in understanding the size differences between biotech companies and pharmaceutical companies. Due to the small number of parties involved in the pharmaceutical process, the average person outside of the pharmaceutical industry does not have an understanding of why viable pharmaceutical products do not make it to market. The COVID-19 pandemic has brought this lack of understanding to the forefront as the average person has waited with bated breath for weekly updates on treatments and vaccine developments.

My study is interesting because it includes interviews with people in the pharmaceutical industry as well as key stakeholders in related nonprofit organizations and insurance companies. Those interviews combined with knowledge from the literature review brought forward the discovery that the advantages of small firms are more conducive to innovation in the early stages and that big pharma companies are best suited to bring the innovation to market. Past studies were hard to compare because some focused on an innovation's novelty and some focused on an innovation's impact.

Literature Review
The Innovation Size Debate

Theoretical views (Gilbert et al. 2006)

Industrialization is relatively recent in human history. Beginning in Britain in the 18th century, factories began to develop where tasks could be subdivided and specialized to enhance productivity (Van Neuss, 2015). An examination of this change was done by Joseph Schumpeter in his books *Theory of Economic Development* in 1911 and *Capitalism, Socialism, and Democracy* in 1942 as well as numerous articles he wrote. Schumpeter in his early work was optimistic about the ability of entrepreneurs to overcome the current market conditions and introduce innovations that would disrupt the market (Schumpeter, 1911, 1949). As he got older and saw some of the horrors of the Great Depression and World War II, Schumpeter started to grow pessimistic about the potential of innovative entrepreneurs to surpass incumbent companies' advantage of scale (Scumpeter, 1942, 2009). As companies scale up, it is very natural for bureaucratic structures to develop to support the size of the operation. Based on Schumpeter's writing, these bureaucratic aspects of a company slow down the development of innovation. As explained by Schumpeter, increasing the size of an organization brings scale efficiencies (1942), but also adds bureaucratic costs.

The relationship between size and bureaucratic complexity is weak, but there is a correlation (Feinman, 2011; Hall et al, 1967). Bureaucracy tends to increase as additional complexities like new fields of study or additional firm locations are added (Hall et al, 1967). As a company gets larger and brings in additional people with more diverse talents, it is necessary to implement more extensive structure. Bureaucracy places people and resources into specific functions and implements a hierarchy that gives power to people based on their placement within the hierarchy. Bureaucracy decreases the flexibility of the organization by increasing the number of points of failure. The number of people with authority to make decisions increases as the bureaucratic structure builds. Each of those people in authority can make poor decisions that could jeopardize the company's effectiveness and success. To compensate for this risk, decision makers are given explicit guidelines which decrease their autonomy or build in redundancy which decreases the efficiency of the system (Zaheer and Bell, 2005). This is exemplified in phrases found in other fields such as Occam's Razor in philosophy or the engineers' imperative to KISS (Keep It Simple, Stupid). It is natural for the winners from the latest disruption to become incumbents and to expand rapidly.

The most iconic refinement of this discussion came from Christensen who divided innovation into two categories: disruptive and sustaining innovations (Christensen et al., 2015). Christensen's division of disruptive innovation and sustaining innovations mirrors Schumpeter's distinction between innovations and inventions (Christensen, 2015; Schumpeter, 1911)Disruptive and Sustaining innovations have different initial paths of development(Bower and Christensen, 1995). Disruptive innovations originating in new or low-end markets are disruptive through the process of displacing an existing market standard or incumbent technology. Disruptive innovations

are the big game changers where the whole market shifts towards a new normal.Disruptive innovations require a company to look at where the market could be in the future and bring a product or service to create that future. Baumol associates small to medium size firms with radical innovations(Baumol,2004). Radical and disruptive have close meanings (Kovacs et al., 2019). As sustaining innovations on the other hand improve upon existing technologies in a portfolio and marginally better than the predecessor product. An example of a sustaining innovation would be going from an Iphone 4 to an Iphone 5. The main features are the same with just a slightly improved screen or battery. Sustaining innovations are found by looking at your existing customers and meeting their needs(Charitou et al.,2003). An incumbent firm can do rather well for itself through sustaining innovation because the incumbent product often stays in the market in some way or fashing(Charitou et al.,2003)

Empirical findings

The innovation-size debate has two main assumptions: that larger companies increase their investment into R&D as the scale up and that the return on the R&D decreases per capita as the company scales up. A general link between size and R&D investment has been found to be consistent and linear (Scherer and Ross, 1990).

Many previous studies looking at this thesis question have looked at patent data to extrapolate the innovativeness of an organization or an individual (Cohen and Klepper, 1996; Kim et.al, 2009; Schettino et.al, 2009). A 2006 paper by G. Scott Erickson found that 43.5% of patents were filed by companies with more than 10,000 employees. That same paper found that 27.14% of patents were filed by small entities (Erickson, 2006). For example, Kim's paper looked at patent productivity that showed slightly higher patent productivity in large firms, but that those differences were negated once they controlled for the number of collaborators (Kim et al, 2009). On the contrary, another study conducted in France of a sample of 121 biotechnology firms did not find that firm size was determinant for innovation (Pla-Barber et al, 2007). The French study did find a connection between export intensity and innovation (Pla-Barber et. al, 2007). A 1993 study found that pharmaceutical companies receive lower returns to scale on R&D productivity (Graves and Langowitz, 1993).

A 2006 meta analysis divided the measure of size used in innovation literature into six categories: direct versus logarithmic measurement, physical capacity, number of employees, measures concerning input, measures of output, and financial resources (Camison-Zornoza et.al, 2006). The number of employees is the most commonly used measure of size (Erickson, 2006; Forés and Camisón, 2016; Chandy et al., 1998).

Measuring size by number of employees is useful because it gives an understanding of how many employees have to cooperate with one another to achieve the desired goal. Each person has to coordinate with other members of the organization. As more people are added, there is more input into the project but also complexity increases.

The other common way to measure size is to look at a company's annual sales (IQVIA, 2019). This method of measuring size is very easy to find because all public companies have to reveal financial information in order to be publicly traded. This measure can also capture the value that contractors bring to the company.

Measuring the innovativeness of an invention is even more challenging than looking at the innovativeness of the organization as a whole. Kovacs, Marullo Verhoeven, and Van Looy in their 2019 paper *Radical, Disruptive, Discontinuous and Breakthrough Innovatio*n argue that authors frequently have different internal definitions of what makes an innovation disruptive. Furthermore, Kovacs and his team contend that two aspects of an innovation are being subconsciously described which are an innovation's novelty and impact of the innovation (Kovacs, 2019). An innovation's novelty can be assessed rather quickly because of its departure from existing ideas. On the other hand, an innovation's impact can only be measured later when longitudinal measures of success such as sales figures or patent citations can be made.

Studies can estimate a patent's novelty by looking at how many previous patents are cited in the citing patent's application. This is still a rough proxy though. As noted in Kim's paper, 50% of the patents cited in their study were for patents more than ten years old (2009). To roughly measure the impact, a researcher can see how many times an invention is mentioned in the scientific literature or one can see how financially successful the product that utilizes the patent is. Measuring the financial success of a patent is somewhat easier for an API (Active Pharmaceutical Ingredient) because it is the only active element in the product being sold. On the other hand, it is more difficult to follow the financial success of patents that cover more complex substances. These measures have not been implemented simultaneously in the studies listed above.

The Pharmaceutical Industry

The beginning of the biotech revolution has its origins in the discovery Watson and Crick made of the chemical structure of DNA. This scientific discovery was kindled and developed within the ivory tower of academia. Watson and Crick's idea would then enter the early stages of commercialization in 1976 when Herbert Boyer started Genentech with venture capitalist Robert Sencourages (Hughes, 2013). The first recombinant DNA product from a biotech firm was released 31 years after Watson and Crick's discovery when Genentech received FDA approval for the growth hormone Protropin in 1984 (Hughes, 2013). One of the most important changes in the rapidly developing pharmaceutical industry was the arrival of biotechnology companies such as Genentech and Amgen that built their businesses by generating natural substances such as proteins for multiple uses such as making synthetic insulin (Hughes, 2011).

The pharmaceutical industry is one of the most regulated industries in the world for good reason as the human body is complex. With hundreds of bodily processes continually ongoing as well as vast amounts of chemicals and microorganisms all responding to each other, the study of the human body can feel limitless. It takes a team of scientists with diverse specializations to create a product that achieves a company's clinical goal. For a pharmaceutical product to be approved for sale, it has to undergo a rigorous series of trials which is divided into four phases which on average cost between 1 to 1.8 billion dollars and frequently take over ten years to

complete. After receiving approval from government regulatory agencies, companies have to gain the approval of insurance companies and doctors for their medicines to enter common use. The incumbents in the industry are traditionally called "Big Pharma'' and include household names such as Johnson and Johnson as well as Pfizer. Standing among these giants are smaller biotech companies which are all competing for funding and attention from the public.

The pharmaceutical industry, which is dominated by some of the biggest companies in the world which regularly create an excess of fifty billion dollars of annual revenue, is a perfect setting for studying this question of size versus innovation (IQVIA, 2019). Every year hundreds of small biotech and pharmaceutical companies throw themselves into the ring to compete with these mega-companies to develop new therapies and medicines.The ecosystem of the pharmaceutical world keeps changing as access to capital and new technologies come along. As discussed in the IQVIA report, emerging firms account for 72% of all late-stage pipeline activity (Adams, 2019). Emerging firms are making it further into the pharmaceutical development process than ever before and are increasingly doing a higher percentage of the research activities (IQVIA, 2019).

According to a report by IQVIA (2019), "Emerging Biotech Firms were the originators of 38 of the 59 Medicines Approved by the FDA (64%)." IQVIA considers firms that spend less than $200 million annually on R&D (research and development) and have less than $500 million in sales annually as emerging firms. These emerging firms account for 72% of all late-stage pipeline activity, up from 61% a decade ago (Adams, 2019). In addition, the abbreviated summary by Adams says, "The top 15 largest companies funnelled more than $100 billion for the first time last year, but the data shows large pharma companies (those with more than $10 billion in yearly drug sales) have seen their R&D share drop from 31% to just 20% in the past decade (Adams, 2019). Based on IQVIA's report the number of drugs being developed outside of large pharmaceutical companies is continuing to increase.

Pharmaceutical Development

Pharmaceuticals develop through a systematic process. Pharmaceuticals are developed in four stages:

- Stage one is discovery and development where, through simulations and modelling software, promising compounds are selected.
- Stage two is when preclinical testing takes place on cloned cells as well as on animals to ensure that a product is safe enough to test in humans. It is usually somewhere in this stage that the company officially patents the molecule if not in stage one.Preclinical testing can take multiple forms such as Systematic Literature Review(SLR), or animal trials. Systematic Literature Review (SLR) is a a technique that uses existing academic literature to determine if a pharmaceutical strategy with similar compounds yielded promising results.These studies are often conducted by universities for around $141,000 (Michelson et al., 2019). Animal trials are the traditional method of preclinical testing (Cook et al., 2012). Mice serve as an imperfect proxy for the effects of drugs on humans (Zielinska, 2010; Greek et al., 2012). Mice trials are estimated to cost roughly $330,000 to conduct properly (Perrin, 2014). The preclinical stage is about ensuring, to the best extent

possible, that you are not harming clinical trial patients in the clinical research phase (Yin, 2012). But it is next to impossible to know the side effects and therapeutic effects of medicines on humans without clinical tests (Yin, 2012).

- Stage three is the clinical research phase where the drug is tested in human patients. The clinical research phase is where there is the highest chance of a company losing their investment.
    - Within Stage 3, there are several different phases:

        Phase 1 of clinical trials tests whether the body can tolerate a drug. It is also during this phase that the maximum tolerable dose is found (Yin, 2012). This stage can vary in cost from 1.4 million dollars for an endocrine drug to 6.6 million dollars for an immunomodulatory drug (Wong et al., 2014). Phase 1 takes place over several months and follows between 20 and 80 patients (FDA, 2014). About 70% of drugs from phase 1 proceed on to phase 2 trials (FDA, 2014). Often the patients in these trials have a dire need for a new treatment making them willing to take the risk of trying a new drug. In cancer patients, these are people for whom existing treatments, such as chemotherapy, have not been effective.

        Phase 2 of clinical trials tests whether the drug has any biological activity or beneficial results. Additionally, there is an initial peek into likely side effects. This is the key inflection point for a company to decide if this is a product worth their effort and resources to push all the way through the approval process. Phase 2 costs and patient size varies significantly based on product field, but often encompasses 50 to 300 patients and costs between 7 and 19.6 million dollars (FDA, 2014; Wong et al., 2014). Depending on FDA guidance, multiple phase 2 trials can be required. Phase 2 is when many small biotech companies try to find a major pharmaceutical company to acquire them or their product (Klueter and Monteiro, 2014). Thirty-three percent of drugs that enter this stage proceed on to Phase 3 trials.

        Phase 3 is the final stage before a company seeks FDA approval for a New Drug Approval (NDA). A phase 3 trial includes 300 to 3,000 patients using the medication in a double-blind trial. The drug is compared to the existing standard course of treatment. Its effectiveness is measured in a wider population. The treatment is monitored for any negative side effects in this wider population as well. A phase three trial costs between 11.5 million dollars for a dermatological study and 52.9 million dollars for pain and anesthesia trials (Wong et al., 2014).

        After phase three, the sponsoring company pays $2 million dollars for the FDA to evaluate their medicine. Approval from the European Medicines Agency is usually pursued concurrently as well, which according to their website costs €296,500, alongside a €106,300 annual fee (EMA, 2021). Alongside lawyers and consultant's fees, the cost of this phase can be quite expensive. The FDA votes on the package instructions that will accompany the new drug. The labelling on the package dictates largely the success of the new drug. If the drug can only be

prescribed to a narrow class of people, such as people with stage four cancer, the market for the new drug will be very limited and the product may be deemed unprofitable. If the labeling is too complex, doctors will not prescribe the drug as frequently as a medication with simple labeling and dosage. Frequently, complex labeling may also make the product not worth the investment either (Werth, 2014).

Phase four trials are initiated, frequently at the same time as phase three trials, to measure the long-term health impact of the new drug. The hope is that the medication will gain approval to be used in additional contexts. Each of these trials enroll several thousand volunteers and cost between $6.8 million per trial for a Genitourinary drug and $72.5 million per trial for a respiratory system drug (FDA, 2014; Wong et al, 2014).

- Stage four is a unique stage. Stage four and phase four occur simultaneously when the product is released to the public and life-cycle management begins on the product. As soon as a company receives the New Drug Approval (NDA), they begin manufacturing and distributing the medication. Based on data from 2018, it takes an average of 13.6 years after a drug is patented for it to be released (IQVIA, 2019). So the project took 13.6 years to make it to FDA/EMA approval. The FDA and EMA almost always accept the same trial data, so it is very rare to not receive approval around the same time (Yin, 2012; Werth, 2014). US and EU patents have a patent length of twenty years once initiated (FDA, 2020; EPO, 2021). Depending on the nature of the treatment there are different lengths of exclusivity periods (See Table I).

Name of Exclusivity	Number of Years	Explanation
Orphan Drug Exclusivity(ODE)	7 years	Orphan drugs are given a longer exclusivity because orphan diseases have smaller patient pools and companies need more time to recoup their investment(Patel, 2019).
New Chemical Entity Exclusivity(NCE)	5 years	The standard exclusivity period for a substance that has not been previously approved(Patel, 2019)
Generating Antibiotic Incentives Now Exclusivity(GAIN)	5 additional years to other exclusivities	This exclusivity is given to new antibiotics in order to address growing antibiotic resistant bacteria(FDA,2017;Patel, 2019)
New Clinical Investigation Exclusivity	3 years	An exclusivity awarded for a drug that is changing doses , treating a new disease or population(Patel, 2019).
Pediatric Exclusivity (PED)	6 months added to existing Patents/Exclusivity	Pediatric Exclusivity is a separate level of protection given to a drug that just gained an additional certification to be given to children(Patel, 2019). Children's clinical trials are often performed later than adult trials because of ethical and health reasons. This exclusivity rewards companies for conducting additional pediatric trials (Yin, 2012).
Patent Challenge (PC)	180 days	This is granted to the first company/companies to file an Abreviated New Drug Application to create a generic variation of a name brand drug(Patel, 2019).
Competitive Generic Therapy (CGT)	180 days	Granted for drugs or therapies that are determined to not have enough generic competition(Patel, 2019).

So the pharmaceutical company has approximately 6.4 years to sell their product before their patent expires. Grabowski, using data from between January 1995 and September 2012 companies calculated that companies 12.9 years after release before a full generic alternative is released and seven years before the first paragraph 4 challenge (Grabowski et al., 2013). A study written three years later by Grabowski and his colleagues showed that the first paragraph 4

challenge for drugs with revenue above 250 million had decreased to 5.2 years after launch (Grabowski, 2016). Once a patent expires and generics are developed, revenue drops very significantly for the brand name drug (Song et al., 2016; Harrison, 2011). An example of this patent cliff was the product Lipitor that lost 59% of its revenue after its patent expired (Chao, 2016).

The Advantage of Large Incumbents

Enormous Capital Requirements

After studying the process to develop a new medication, it is obvious that very large amounts of capital are required to progress all the way through the development process. The challenge of commercialized scientific research is that there are massive capital requirements. A study that looked at proprietary data from a selection of small and large pharma companies found the research cost of a new pharmaceutical compound to be out of pocket to be 1.3 billion, but after factoring in a discount rate of 1.5% and post approval costs, the final cost estimate is 2.8 billion (DiMasi et al., 2016; DiMasi et al., 2020). As a firm progresses through the research pipeline, the cost increases exponentially. The last billion is usually spent in phase three trials when enrolling thousands of participants, each of which costs an average $41,117 dollars to treat with the potential product (Sertkaya et al., 2016). During phase three, pharmaceutical companies also begin setting up production facilities and hiring a sales staff to market the product.

The manufacturing is expensive due to drug complexity and extreme cleanliness standards. These billions of dollars of money can be very hard to raise for a startup, or small company, because they have very few assets to secure a loan beyond their patents, and even those patents could become worthless if the trials fail or a patient treated with a previously developed medicine sues the firm. More risk-oriented investors such as venture capitalists can become involved, but they prefer equity which is frequently more expensive in the long run compared to straight debt.

On average, pharmaceutical companies have 12.9 years from market entry before generic drug manufacturers release a generic competitor to their product (Grabowski et al., 2014) . This is a relatively small window for companies to give a desired return to investors. According to a 2011 paper, pharmaceutical companies face interest rates 2.8% higher than the industry standard formula, Capital Asset Pricing Model (CAPM), would predict (Giacotto et al., 2011). This means that the estimate of 2.8 billion dollars put forward by DiMasi et al. (2016) is potentially an underestimate of the full financing cost because CAPM was used to estimate their financing costs. Giacotto et al. argues that the higher interest rate creates strong capital flow issues for pharmaceutical companies because they have to pay a large premium for financing their deals (2011). Giacotto et al. (2011) suggests that the premium lending rate above CAPM is due to high research costs and high failure rate of pharmaceutical projects which create a volatile investing environment (DiMasi et al., 2016; Wong et al., 2019).

That volatile investing environment then makes an investment less attractive and thus a higher interest rate than the CAPM is levied (Minton and Schrand, 1999; Giacotto et al., 2011). A

2015 study suggested that the high lending cost mentioned by Giacotto et al. (2011) was due potentially to an information asymmetry between the pharmaceutical companies and the lenders (Chit et al., 2015; Hubbard, 1997). This hesitancy makes intuitive sense because pharmaceutical companies do not want to reveal their strategies and banks do not want to be left with the bill of a multi-billion dollar failure (Wong et al., 2019). Giacotto and colleagues suspect that the 2.8% premium cost above the CAPM rate is even higher for biotech companies based on their relatively high potential return or beta (Giacotto et al., 2011; Theodossiou et al., 2009).

Biotech companies meet the HTV (Hard-to-Value) criteria because of the long development time of their pharmaceutical products (IQVIA, 2019) and their dependence on intellectual property for their value. Being hard to value makes it very difficult for young biotech companies to acquire capital (Waagø, 2004). Creating a valuation for a biotech company is very challenging which makes private equity or venture capital a very useful tool for a company to signal their value (Janney and Folta, 2003). Signalling allows companies to prove at least imperfectly how much their ideas are worth to the market and access capital (Janney and Folta,2003).The long development time for biopharma means that they are dependent on outside capital until they are approved. A paper looking at 254 biotech firms that underwent an IPO found that a university affiliation increased investor sentiment,increased their valuation and the probability of the biotech receiving M&A requests (Meoli, Paleari, and Vismara, 2011).

Failure Absorption

The second major cost is absorbing failed drug candidates. Forty-five percent of non-oncological drug candidates fail in Stage 2 of FDA testing (Wong et al., 2018). When a drug candidate fails in trials, very little of the money spent is reclaimable because there are no physical assets like land to sell. At stage two, a company has spent several years paying for preclinical testing which costs at least few hundred thousand dollars, paid for a clinical phase 1 test which costs a minimum of 1.4 million dollars (Wong et al., 2014), and most of the cost of the phase II trial which costs a minimum of 7 million dollars (Wong et al., 2014). Absorbing the cost of a failed drug is expensive and frequently hard to quantify in traditional investment risk strategies.

The traditional method of handling risk by diversifying your portfolio is very challenging for a Biotech startup because funding multiple drug candidates especially beyond Phase I is cost prohibitive. Beyond phase I clinical trial costs increase to a minimum of seven million dollars and can reach up to fifty million dollars (Wong et al., 2014). Additional money especially in earlier stages originates with venture capital funds (Huggett, 2012). This leads many small companies to place their hopes in one drug candidate or product. If that product fails, the whole company falls apart (Werth, 2016). Even a less severe event such as the FDA requesting additional testing can lead to a funding crisis or total company failure.

The largest five firms, based on market value of equity, possess 71% of the total industry capitalization. The top ten largest firms possess 90% of the pharmaceutical industry capital (Giacotto et al., 2011) leaving the final 10% of industry capitalization to leverage for investing. Large Pharma companies usually have large capital reserves to absorb potential costs and to invest in multiple products simultaneously.

Threat of Acquisition

Hard to Value companies that are dependent on intellectual property, key personnel, or long term future earnings are subject to market devaluation and possible takeover attempts (Ali et al., 2012; Humphrey-Jenner, 2014). Many startups fall prey to large competitors because when they encounter financial trouble (Danzon et al., 2007). Vertex faced this threat early in their company history and had to generate new leads in order to keep investors from dragging their stock price down (Werth, 2016). The long investment window of pharmaceutical development makes biotech companies especially vulnerable to investor flight (Abate, 2013; Pelz, 2011).

Connections with Other Companies

Established companies have existing relationships in their field with suppliers and buyers. This makes it easier for their adoptions to potentially enter the market (Obal, 2012; Obal et al, 2016). When disruptions come, suppliers and buyers reach out to existing partners to mediate how to react to the new threat (Obal, 2013). These relationships could be strong enough that the first movers and inventors have to seek out relationships with incumbents in a knowledge market (Gambardella et al., 2010). This includes trust with regulators which can be a massive advantage for incumbents compared to startups, especially in countries with culturally low risk tolerance (Obal, 2012; Chandy et al., 2000). A survey conducted amongst Australian firms found that network effects determine differences in innovative ability (Rogers, 2004).

Relationship with Regulatory agencies

A possible factor that could favor large pharma companies would be a relationship based on previous successful cooperation This can be seen when well-respected incumbents, such as Merck, go through less rigorous scrutiny from regulators regarding their product. This is discussed in *The Antidote* where Merck's HIV product received a unanimous 18-0 approval from the AdComm despite having no drug interaction studies done for antidepressants and a complex regimen that was described by a panel member as: "You need to be somewhat of a Talmudic scholar to prescribe it" (Werth, 2014).

Factors of Bureaucracy that Inhibit Innovation

Potential Product Cannibalization

Big pharma faces several challenges that small biotechs do not. When incumbents already have products in the marketplace, they are disincentivized from pushing a disruptive innovation forward that could potentially replace their already released products. Due to the tremendous development time and costs, companies have a very narrow opportunity to make a profit on their medicines. Emerging companies do not struggle with this disincentive because they do not have a wide patent history or existing portfolio to protect. Many biotechs frequently have a singular focus and product, so they do not have to protect other products.

Chandy and Tellis (1998) even argue that a willingness to cannibalize is a greater predictor of radical product innovation. In particular, the presence of internal markets, influential product

champions (intrapreneurs), and future product focus can allow a firm to overcome a fear of cannibalizing existing products and move forward with radical innovation (Chandy and Tellis, 1998;). Internal markets can lead to more innovation by having teams internally compete against each other (Chandy and Tellis, 1998). This, however, leads to losses in scale efficiencies because key resources have to be duplicated for each team. In regard to the presence of intrapreneurs, the question becomes whether intrapreneurs are more likely to succeed within a bureaucratic organization.

Organizational Inertia

Organizations have a collective memory embedded in their employees. As an organization succeeds in certain methods, capital is acquired and employees become accustomed to particular methods(Barnett et al.,2008). This organizational inertia prevents a company from adapting to discontinuous innovations(Junarsin,2009).

Stability

Bureaucracy leads to stability which investors prize. Stability is associated with exploitative innovation (Jansen, 2006). To achieve this stability, additional bureaucracy is introduced. This is often called "bringing in adults". The original team steps down and is replaced by people with more experience from existing companies. In Vertex, this was the replacement of the founder Joshua Boger, who had been there for twenty years, with Jeffrey Leiden as CEO. This cultural change is initiated by investors to increase stability of the company and to protect their investment. Volatility in an investment is unattractive for investors because it increases the risk and makes it harder to sell large quantities of the stock. Due to the cultural changes, many of the star scientists and managers such as Bink Garrison, Ken Boger, Bo Cumbo and Ann Kwong left the Vertex to join smaller companies (Werth, 2014).

Political Risk

Governments in the USA and Europe have a preference against oligopolies and monopolies (Atkinson et al, 2018). Large companies are subject to more scrutiny by government agencies. Their size often leads them to being heavily regulated. This can lead to unexpected pushes by regulators to change an incumbent's corporate structure or to divide the company. These unexpected shifts reduce the benefit of scale by removing horizontal integration and their associated scale advantages which leads to a net loss in innovation.

Legal Risk

Almost all pharmaceutical companies have an external or in-house legal team that applies for patents and defends against lawsuits . When a company is sued for a drug's side effects, the value of the whole company is at risk (Wagner, 2006). Wagner discusses how the perceived risk of a product such as asbestos affect related industries such as transportation companies' ability to access insurance products (2006). This fear can have a negative effect on a company's willingness to invest in innovations (Galasso et al., 2018). Galasso and Luo's paper found that medical device patenting significantly decreased after the high profile bankruptcy of Vitek due to a product liability lawsuit (2018).

A legal department concerned about potential liability issues could delay critical deals and slow pharmaceutical development by months. This leads to lost time and misallocation of scientists that could be working on valuable activities. Scientists who are the primary drivers of pharmaceutical development are forced to delay what they are passionate about. Sometimes the window for the release of a medication is missed completely.

Risk Tolerance of Executives

Frequently as a company grows larger, risk tolerance becomes lower. In major conglomerates such as Monsanto and GE, the people making decisions have access to quicker and lower risk opportunities. A possible mechanism of this could be incorrectly applying discounted cash flow and Net Present value (Christensen, Kaufman, and Shih, 2008). Managers using a depreciation schedule are less incentivized to adopt a new technology because they will have to take a writedown on a previous investment(Christensen, Kaufman, and Shih, 2008).

An additional factor in this problem is the average tenure of S&P 500 CEO which has decreased to only five years (Marcec, 2018). Based on this average, a pharmaceutical product will be overseen by at least two CEOs during its development and rollout. Each of these CEOs will bring a different leadership style and risk tolerance to the table. Frequent strategic changes can put high investment pharmaceutical projects at a high risk of being cancelled. The first CEO may have been willing to take a risk for a product and the succeeding CEO may find the medication too risky to continue development.

A study found that there was a link between CEO tenure and exploitative innovation(Li and Yang, 2019). Exploitative innovation is usually much more incremental less likely to cause disruptive changes

Star Scientists

An opportunity that large bureaucracies frequently miss is star scientists. According to Zucker and Darby in their paper, *Star Scientists and Institutional Transformation*, star scientists produce 22 times more productive patents than a normal scientist (1996). Zucker and Darby further explain that incumbent firms are very slow to develop relationships with star scientists while they are still in university which leads many star scientists to start or join bio-pharma startups. These startups benefit significantly from catching university stars early. Zucker and Darby go even further stating, "This is too short a career for the scientists to be hired for any possible halo effect. Indeed we think many of these scientists became stars only because of the very substantial productivity effects of working with NBEs (New Biotechnology Enterprises)." Subsequent articles have noted that this relationship is much more nuanced (Colen et al., 2014). The study by Colen notes that the benefits of star scientists requires that the star scientists be willing to engage with the corporation in applying the scientist's basic research into an application.

Lack of Recognition

Large companies assign dozens of people to work on a product over the course of the product's development period. Only a handful of those people are noted on patents or in the

accompanying articles. This prevents junior members from receiving credit for the discovery which can stall their careers. Additionally, ambitious young scientists are sometimes given only middle authorship which sends an ambiguous signal to the academic world about one's accomplishments (Paul-Hus et al., 2017). Middle authorship can be given for roles varying from significant contributors who wrote the whole article to the assistant who only helped clean test tubes (Paul-Hus et al., 2017). Future employers must rely on the potential employees' word concerning their level of contribution to the project. More importantly, ribbon, or recognition, is a significant motivator for scientists (Lam, 2011). Scientists working for ten years to develop a new drug want to receive proof that all of their efforts were important and recognized. This watering down of credit can leave deep resentment and lead to incumbent companies losing valuable contributors.

Knowledge Siloing

Large incumbent corporations frequently have strong knowledge silos where top researchers protect their role by not sharing their knowledge with young researchers, which causes succession issues. This is in comparison to small biotechs where team members are much more likely to work cooperatively and thus naturally pass on intellectual knowledge. In less malicious situations, siloing reduces the ability for organizations to be flexible (Waal, Weaver, Day, and Heijden, 2019). The complexity of developing medicines makes flexibility highly valuable in the biotech/pharmaceutical sector. If the formulation team does not have a good relationship with the active ingredient team, potential changes can harm the effectiveness of the medicine in trials. As Albrecht says, "Somehow, when the "big idea" lands in the various organizational silos, it immediately gets localized and diced up into parts that no longer fit together as a whole" (Albrecht, 2002, p.3). If one is interested in making major discoveries, knowledge silos can be a major handicap. While these problems can be addressed, it takes intentionality to fix them (Waal et al., 2019).

Lack of Input on Projects

Bureaucracies often force direction from the top of the organization which is in opposition to the fact that accomplished scientists desire to choose their own research topic (Conti, Gambardella, and Mariani, 2013). Accomplished inventors (defined as people with at least one published patent) are less productive when goals are centrally planned as happens in large pharmaceutical companies (Conti et al, 2013). Scientists may have gotten into the field for very personal reasons such as curing breast cancer because they lost their own mother to breast cancer, so the bureaucratic habit of setting goals from the top down can be very frustrating for the star scientists.

Internal cooperation

According to a Royal Society of Arts report based on information from the UK Workplace Employment Relations Study, "Micro business employees score highest on most indicators of job satisfaction, including influence over their job, involvement in decision-making and good relations with management" (Dellot, 2015). Inventors are willing to make a significant wage reduction to maintain control of their projects (Aghion et al., 2008; Stern, 2004). Inventors are very interested

in being involved with decision making because they are very passionate about seeing their products make it to market. In emerging biotech companies, the team is frequently under fifty people which allows every employee to have a personal relationship with one another. This high trust environment allows people to be vulnerable about results and leads to organic teamwork. Cooperation within smaller companies is more organic due to people's limited ability to maintain relationships(Panda and Nayak,2019). Panda and Nayak go on to argue that keeping the firm small allows people to organically cooperate(2019)

Specialization

Bureaucracy frequently leads to specialization. Scientists who were trained to do many diverse tasks in university are assigned to a single routine task or set of tasks. employees can feel like their potential is being underutilized and this has been shown to be harmful to innovation(Länsisalmi et al., 2004). There frequently can be coordination issues as a firm employs increasingly specialized employees (Brusoni, 2005). Startups, and emerging firms in general, offer significantly fewer organizational boundaries. Members of an emerging firm have to perform several functions because their size dictates that they cannot have the same level of specialization as a large corporation. This leads to employees retaining and regularly using a wider array of their skills. When cultivated, that skill development can increase the bench strength of the company. Bench Strength in management circles refers to the fact that a company is not reliant on a single employee to perform a function. An example of this is if a key engineer is sick for a week, the company is still able to keep the project going because his assistant has a solid understanding of the project.

Literature Review Overview

This section has brought together a wide selection of discussion in management together to act as a preparation for understanding the academic community's current understanding of innovation in small and large firms. A discussion has also been given of how previous studies have sought to answer the size discussion using patent data and how attempts have been made to measure impact and novelty (Kovacs et al, 2019). Possible theoretical applications of these concepts have been adapted to how they may appear in the pharmaceutical industry as a whole.

Empirical Study

Methodology

The researcher will seek a convenient sample of professionals in the Pharmaceutical industry with over fifteen years of experience in their industry and experience working in an executive role. Participants will be contacted by email or LinkedIn mail to complete a thirty to forty-five minute interview. Demographics such as race or national origin will not be a variable in this study. Twelve participants will be asked. Small participant research is helpful because it allows

a researcher to look deeply into each participant's experience and ask questions tailored to their personal story and experience.

Potential interview subjects will be found through professional social networks such as Linkedin and contacts from previous academic work. Their resume will then be assessed to determine if their work history matches the interview requirements. All of the interviews will be held online from home offices to ensure a neutral location. Home offices allow participants to feel safe from potential professional repercussions or coercion and hopefully will allow the interviewees to be more honest and open.

Brief Biographies of Research Subjects

1. Dr. Annette Bakker was interviewed on April 30th, 2021. Dr. Bakker studied biochemistry for her PhD. She worked for six years at Johnson and Johnson before starting her own biotech company. Nine years ago, she joined a university as a lecturer and shortly afterwards, Dr. Annette joined the Children's Tumor Foundation (CTF) where she worked as a chief scientific officer before becoming the president of the US Children's Tumor Foundation. The Children's Tumor Foundation recently started a European branch where Annette is the vice president. In addition to her work as a lecturer and nonprofit leader, she also is a board member of New York Bio.
2. Dr. C was interviewed on April 27, 2021 via Zoom. Dr. C holds several graduate-level accreditations in biology and chemistry. She started her career with a small biotech firm. After five years at a small biotech firm, Dr. C and her husband started their own biotech firm. They have operated their own firm for over twenty years. As a research team, they have registered over 220 patents and trademarks.
3. Mr. D was interviewed on April 14th, 2021 via Google Meet. Dr. D is a biochemist by training. He holds a masters in Biochemistry. He has worked in the pharmaceutical field for over twenty years. His first job after university was as an early employee for a small biotech company creating a particle intended as a food additive. After leaving this small biotech company, he joined a biotech company that was being set up as a greenfield investment by a major chemical company. Later on, he joined the team of another major chemical company's biotech division consulting on multiple projects.
4. Dr. G was interviewed on April 12th, 2021 via Google Meet. Dr. G is trained in biochemistry. He worked in a university lab for a few years after receiving his Ph.D in Chemistry. He was then approached by a biotech startup to be one of their first hires. He has worked with this startup for close to two decades and currently is their Chief Scientific Officer.
5. Dr. K was interviewed on April 14th. He completed his PhD in Organic Chemistry. He worked for a major incumbent pharmaceutical company and quickly rose up through the ranks. He then joined a recently acquired subsidiary company. Following his experience at the subsidiary, he worked at an established biotech startup. He now works as a consultant and is looking into starting his own company.
6. Mrs. L was interviewed on April 27th, 2021 via Google Meet. Mrs. L studied Psychology in her undergraduate studies and holds a master's degree in computer science. Mrs. L spent

four years doing clinical psychology work and publishing studies. After this, she joined a major insurance company designing medical databases. After success in her first insurance company, she was hired by a rival insurance company. During her twenty years at this major insurance company, she ran health care innovation as well as clinical service departments. She now serves on the board of directors of multiple health care companies. Additionally, she serves as a consultant that aids clients in improving their organizational design.

7. Dr. M was interviewed on April 19th. Due to time and privacy constraints, only a small selection of questions were answered. Dr. M started as a biochemist in a very prominent biotech firm. After rising up the ranks, he was offered the chance to be the CEO of a spinoff company. After this he returned to his original company for a lengthy period of time. He now works with major VC firms and is active on half a dozen biotech firm boards.
8. Mr. M was interviewed on two occasions December 11th, 2020 and May 30th, 2021. Mr. M holds a masters degree in chemistry. Initially he worked in a medium sized biotech company for 5 years before transitioning to a job at a major chemical company. Over time he was given more responsibilities and eventually ran his own department within a chemical company's biotechnology formulation division. His work included API development, but was focused on developing the "inactive" ingredients in a medicine.

Ethical Considerations

The participants in this study were not compensated for their time. All of them are rather successful in their careers, so any financial incentive would have been implausible on a student budget. The participants also did not receive any other benefits beyond a chance to verbalize their internal understanding of their field. To avoid any backlash in their workplace or among peers, any identifying information has been removed from their comments by default unless a participant explicitly asked for their name and organization to appear within the thesis.

Research Design

A Google meet link will be sent. If the participant is unable to use Google Meet, a phone call will be arranged. The Google Meet account provided by the school has the included ability to record a call. The recording will allow me to have a better transcript and for me to be more emotionally responsive during the interview. At the beginning of the phone interview, I will confirm that I am talking to the correct person. I will explain to the participant that their participation is completely voluntary and ensure that no coercion is involved. Any coercion or involuntary answers would be unethical as well as corrupt the quality of the data. I will note that any answers given will be anonymized unless the participant explicitly desires that their participation be publicized. I then will ask the participant if I can record the meeting solely for my personal use. After consent is given, I will begin the recording. The first few questions are warm-up questions to confirm the person's work history and education experience. Professionals on LinkedIn do not always share their full work history, so asking questions regarding their work history in the interview can provide additional details and insights into their experience. Educational experience increases a participant's credibility as well as can open up their experience to working in an academic lab.

Then questions about each of their workplaces will be asked, particularly asking about knowledge management and resource availability. The questions will be customized to the person's work experience. For example, an innovation manager may not have had experience in sales so those questions will be skipped. After the questions are answered, I will ask if I can contact the interviewee later to clarify comments or ask additional questions. I then will finish the call by thanking the interviewee for their time and expertise. Eight interviews between 30 and 45 minutes each were conducted with high-level leaders in the pharmaceutical field. Interview subjects were chosen that had at least fifteen years of experience and had extensive experience in a management or leadership role. Many had worked their way up from scientist to management/CEO/owner positions. These experiences allowed them to have a balanced perspective on the industry as a whole. Those with leadership experience were chosen because they had experience making decisions and had access to the relevant information to make those decisions.

Intervention Protocol

The interview process will not be a significant intervention because the calls will take place outside of the workplace on the participant's personal time. It will not prevent the participants from executing their jobs.

Interview Instrument and Protocol:

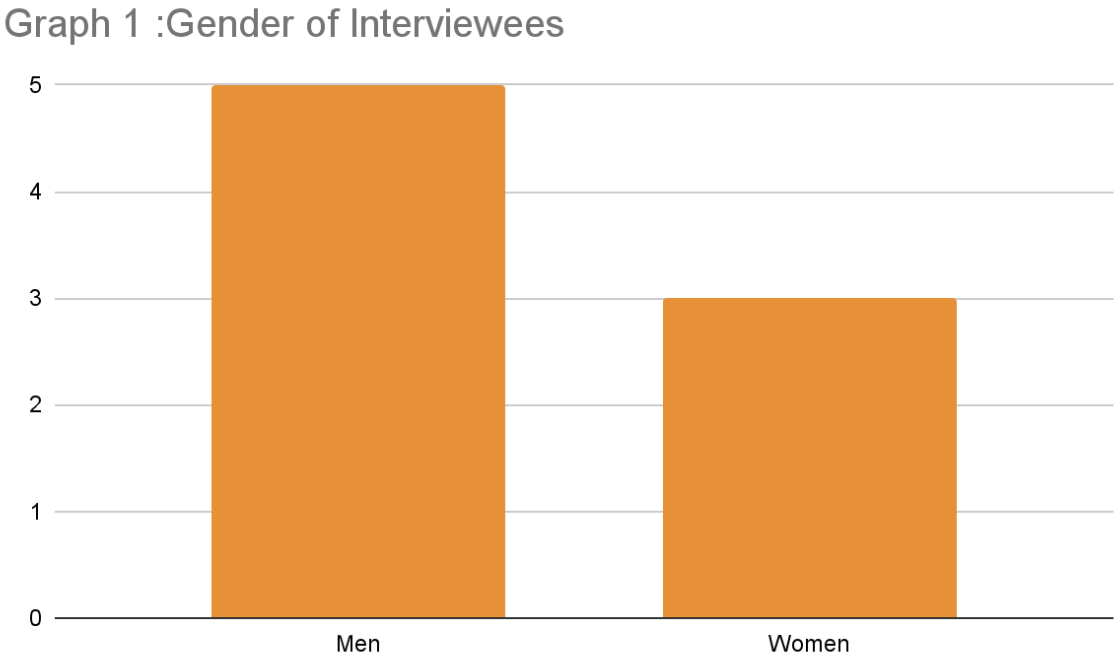
Focus interviews were used as the interview instrument. Focus interviews concentrate on the interviewee's experience and the interviewer emotionally responds to the interviewee. This interview format was used because the subject matter of this encompassed a wide set of factors of which not all interview participants would have expertise from which to comment. An additional factor was that public knowledge about a person's work history may not encompass all of the interviewee's relevant experience.

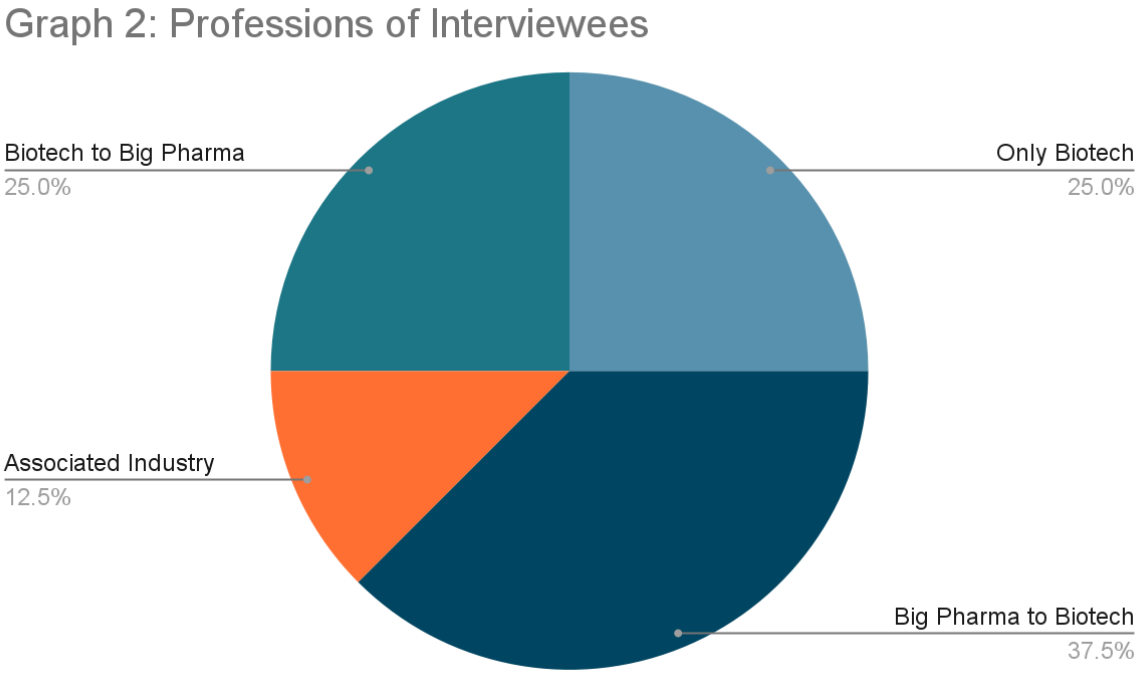
Data Analysis Strategy

Comments in the interview will be sorted into relevant topics. Those comments will then have identifying information removed. After removing the identifying information, I will sort the associated topics under meta-categories.

Sample Description

Due to the pandemic, I fell short of my goal of twelve interviews. Eighteen were invited to participate, but only eight professionals were willing to be interviewed. The interviewees all were prominent in their firms, which legitimized and made significant their comments. As seen in Graph 1, a close number of men and women were interviewed to get a diversity of opinions. Further, a balance of people with varying experience in big pharma and biotech was found as shown in Graph 2. It was important to find a variety of both of these factors to assure a more reliable result. The interviewees' movement into biotech is relevant to the concluding discussion.





Data Analysis Strategy

The interviews will be coded in order to generate key themes and create relationships amongst them. The first level coding will look at the instinctual labels. Those labels will then undergo a second level of analysis where meta themes will be brought out from the initial coding. In table I, the major categories of cooperation,

Data Analysis and Coding:

First level Coding: Initial labels

Cooperation with Academia
Cooperation with other companies
Cooperation internally
Financial Challenges
Organizational Complexity
Purity
Self-selection of scientists
Legal Challenges

Second Level Coding: Relationships between the themes resulting from the primary level coding.

Table I

Cooperation	Cooperation with Academia Cooperation with other companies Internal cooperation Knowledge Siloing Legal Risk Relationship with Regulatory Agencies
Size	Organizational Complexity Self-selection of scientists Financial Challenges

	Initiative Equity in the Venture Financial Challenges Flexibility
Predictability	Reliability Purity

Major Categories of Organizational Components

Cooperation

Cooperation with Academia

Within the areas of study, cooperation with academia was a topic that all the interviewees referred to. Mr. M explained that biopharma companies cooperate with academic institutions in order to get really detailed knowledge on their products. The FDA and EMA evaluate drugs based on whether a company can show how a drug has a certain effect on the body and why that certain effect happens. In Mr. M's opinion, many scientists working in industry, especially in larger companies, do not have time to research the "nitty-gritty" details because of the tight deadlines common in the pharmaceutical industry. These critical details are often found only through very narrow research that is more commonly found in a Biotech or academic setting (Mr. M, Dr. K).

Dr. K said that it was very nice to collaborate with universities as a scientist, but it was very hard to handle from a project management perspective. He explained that this is because academics and scientists working in industry have different goals and responsibilities. This difference of incentives made Dr. K feel like he was herding cats when he was working with academic scientists. He further explained that academics tend to be focused in more directions than scientists working in the industrial sector who can focus solely on research and development. Dr. Bakker also touched upon the different incentive structure between academic scientists and scientists in industry. Dr. Bakker believes that incentives need to be realigned between academia and industry. Right now, many academic accomplishments are not making their way into practical applications. The academic system in her mind is not rewarding researchers for making viable connections with the pharmaceutical industry. What seemed to really frustrate Dr. Bakker was all of the potential knowledge that was being left unutilized or underutilized because the incentive systems did not match up.

Mr. M disagrees slightly with Dr. Bakker in that he has found that in the last five years universities have become much more commercialized because many universities have started licensing departments to reap the rewards of their professors' research. The professors themselves are still very open to cooperating through research. Mr. M has had five or so research agreements with academic institutions take two years to be processed by his large firm because of contract disputes over licensing costs and initial payments for research. A two year hold on a research agreement can be very disfavorable because Ph.D students may only be at a certain university for a few years. This does not take into consideration delays from related projects having unrelated questions or delays in product release. This intuitively could cause issues because it creates additional actors in a process that will slow down completion time for deals and reduce the ease of access. Overall, the interviewees said that cooperation with academia is very beneficial and they enjoyed it but it has grown increasingly difficult due to academic institutions having developed licensing departments and commercializing their ideas.

Cooperation with Other Companies

Another topic that was mentioned by the majority of interviewees (five) noted that they frequently cooperate with other companies. Dr. K said that both the incumbent companies and the small companies that he worked with very frequently cooperated with rivals to develop new products. It is necessary in scientific inquiry to work together with others.

Dr. M has found that biotech entrepreneurs often leverage pre-existing connections from their previous jobs or from their venture capital firm. These connections can help new entrants overcome the incumbent advantage of developed professional relationships. mentioned in Obal's 2013 paper. For startups without existing relationships, developing connections can be a big hurdle to overcome. Mr. M has found that "the bigger they (pharmaceutical companies) become, the more difficult (to become accepted), so if you are not there as a partner in the early stage, it's more and more difficult, the bigger they become".

Dr. C's biotech company had several challenges in their early years gaining clients and obtaining funding. Due to the small size of Dr. C's company, they needed to cooperate with other companies and organizations to do even the preclinical studies. Dr. C noted that as her company sold their first few discoveries and developed relationships with companies in their industry, funding became much easier to obtain. Their reputation and previous inventions could be used to fund their future research and to compensate their contractors.

These financial challenges can even extend into companies not wanting to preorder goods or caution around long-term contracts. Mr. D recounted an event from his time at a biotech startup when they were given a less advantageous short-term contract because the buyer was concerned that the startup would go bankrupt before the completion of the contract. The buyer did not want to have a long-term contract with their startup company even though Mr. D's biotech company had been able to prove that there would be no manufacturing capacity issues. Their customer was impacted by previous experience when they had issues with biotech companies going into bankruptcy during their relationship with them. The customer had trouble evaluating new companies' long-term viability.

A further result for Mr. D's company from their lack of industry connections came when a major food company suddenly came onto the market with an improved version of their existing product. The major food company's sustaining innovation was that the low end disruption of Mr. D's biotech company was blocked out because the sustaining innovation was significantly cheaper without a drop in quality. Mr. D's small biotech company could not compete with the lower price point. This resulted in a major pivot for the company. Mr. D argued that if his company had had deeper industry connections, they would have been able to pivot to a better product or change their strategic approach.

Dr. Bakker discussed how government agencies and potential buyers of a biotech's product look at a biotech start-up's big pharma partner as a sign of legitimacy. Big pharma typically does not want to get involved until relatively late in the process though, usually after pre-clinical testing. Three of my interviewees who had worked in big pharmaceutical companies agreed that their companies looked into licensing and funding arrangements as early as the preclinical stage (Mr. M, Mr. D and Dr. K). This conflict can be somewhat mediated once you understand Dr. Bakker's current job as the chairwoman of a nonprofit focused on curing a childhood cancer called neurofibromatosis. Cancer drugs have some of the most expensive clinical trials (Wong, 2014) and lowest success rate among all therapeutic areas with a 3.4% chance of success (Wong, 2018). Based on the high failure rate and clinical trial cost, it makes sense that pharmaceutical companies would be hesitant to invest at an early stage in Oncological drugs to treat cancer.

Internal Cooperation

An overarching theme of the interviews was that corporate life in large pharmaceutical companies was much more structured and specialized than in biotech companies. Some of the interviewees found the structure and specialization beneficial and comfortable while others found the structure stifling and detrimental to pharmaceutical development progress.

According to Dr. Bakker, "The main difference between big pharma and biotech is that big pharma has a lot of money so they can put one person per task if you want. In biotech you don't have that luxury, so you really need to hire people with a different mindset of rolling up your sleeves and getting work done." Specialization allows people to focus on one single thing at a time. Dr. Bakker continued by saying, "That is in fact what you need in a biotech. I'm not saying one system is better than the other. Having an ultra-specialist in a micro domain can sometimes be great, but I think it's only great if you connect all of these ultra-specialists. I think the proof is that there are a lot of pharma companies now who are buying drugs from biotechs because they don't have the creativity and the innovation in their companies."

Mr. M found that frequently cooperation with other organizations goes more smoothly than within the company. He said, "Even if your customer is convinced, you still have to convince your internal CEO and upper management at different levels, because the higher you go, the less risk they want to take." He has found it really difficult to get projects accepted overall. Mr. M has found that you really need a very solid business model, before you can start selling the project in-house.

Dr. G added to this line of thinking when he focused on small company advantages and said that they kept their company small so that they could keep the team small enough to have organic connections with one another. In smaller organizations managers are continually reminded

to make sure that their subordinates' contributions are recognized. Dr. G also encourages each employee to be as self-motivated and self-directed as possible.

Knowledge siloing

The common thread amongst all the interviewees was that knowledge siloing was often the result of people not having psychological safety in their teams. Mrs. L says that knowledge hoarding is very common when she does consulting work with small biotech companies. Mr. M frequently found employees hoarding knowledge because they are afraid of losing their job if others could do their tasks. Fear of job loss is indicative of feeling unsafe in the workplace.

Part of this hoarding is because people are afraid that they will not receive credit for their ideas. Mr. M had a number of stories from his work experience when coworkers would only share data when they could be sure that their contributions would be noted.

Dr. Bakker accredits knowledge siloing in pharmaceutical companies to having scientists working in micro domains and not being able to communicate well with each other. "They (pharmaceutical companies) have so many ultra specialized people that don't understand each other so you almost get a Babyonian situation where you have all these smart cookies that are not able to work together because they genuinely don't understand each other's languages."[1] If this knowledge is not shared or is not shared succinctly, scientists are unable to cooperate efficiently. This also causes development issues because employees get sick or retire without passing on their knowledge which can cause lost knowledge and slow processes down to a grinding halt. Mr. M believed this phenomenon to be relatively common. At pharmaceutical conventions, he frequently heard people from other companies having similar issues.

Legal Risk

The only interview subject that directly addressed legal issues was Mr. M. He said, "The common joke is who is running the company - the managers or the legal people? There were legal people who define where it's safe to move, and they don't want any risk, but to develop completely new projects, we need to take some risk." Mr. M described it as an industry-wide problem, the struggle between the legal department and those who want to innovate quickly. He feels that the bigger the company is, the more legal people are thinking they need to make decisions. The issues incurred when legal teams are involved is much more common in the large pharma setting since biotechs cannot afford to have a whole legal team devoted pursuing these issues.

Relationship with Regulatory Agencies

Only Mr.D brought up the relationship between regulatory agencies and large pharmaceutical companies. Mr.D described the relationship between regulatory agencies and large pharma companies as pretty healthy. Mr.D attributes this trusting relationship to employees switching between jobs in large pharmaceutical companies and regulatory agencies pretty frequently. This frequent job switching could lead to organic relationships between employees.

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[1] I believe Dr. Bakker was referring to the biblical story of the Tower of Babel.

Former FDA/EMA employees who left for industry would have a good understanding of what regulatory agencies are looking for in a drug candidate. The whole approval process relies on pharmaceutical companies being transparent and virtuous about their data to receive approval.

Size

Organizational complexity

The overall message of the interviews was that size frequently was a deterrent to innovations, but that proper structuring could significantly decrease productivity loss. Although all interview subjects touched on organizational complexity as an element in their innovation process, Mrs. L, who is an expert on matrix organizations, focused much more on it than other interviewees. She says that matrix organizations are challenging to do well. "It's a balancing act in any large organization to figure out how to let innovation happen." Mrs. L has found in her work that a well-structured matrix can actually increase the speed of innovation though. "Actually if you structure the matrix, it [innovation] can go faster because part of what you do in the matrix is ... one group is really good at compounding, and one group is really good at looking at the ingredients, all the bits and bites that go into these things, you get that deep expertise and you let them work together as a team and you reward them as a team. That to me is the most powerful thing." The key to this is structuring decisions and resources so that people do not hoard resources.

Mrs. L continued, "That said, I had to put a pretty formal program into place to enable innovation across teams. It feels a little hokey at first, but then you get pretty significant recognition and you see some big impacts, then it's pretty attractive." Mrs. L noted that you must limit pocket veto though. The pocket veto is the ability of a manager to stop an action through inaction. She also noticed in the companies she worked with that as knowledge hoarding decreased, innovation across teams increased. The trick is to achieve healthy meritocracy.

The organizational complexity proved a blessing and a curse for Dr. K. He left his job at a major incumbent company because he found most of his time was being spent on administrative work. As he said, "You have to feed the beast." As he was beginning his career in a large pharmaceutical company, the organizational complexity of the company had provided guidance on how the job would be carried out and had redundancies in place to make sure any mistakes he made would be quickly caught and not have major ramifications on patients or the company. Heavy bureaucracy allows scientists to have regular hours and learn in a safe environment. When asked about his time at the recently acquired biotech company, he said that the company still had an independent biotech feel and that their strong management team, which is one of the strongest management teams he had worked with. This was due to their matrix organization, which had two management teams approve projects for scientific merit and their marketability. He said that this was very empowering and encouraged an independent can-do mentality.

Mr. D chose to keep the organizational complexity simple. He was able to handpick a very small core of about five people that would be part of his leadership team for a new site that he was invited to initiate and then those five were able to handpick about 20 more people. That was going to be the full group at this site. Mr. D continued:

> So while I was part of a much larger organization, and I got to interact with many colleagues in Germany and abroad, at the same time, it actually felt like I was working for a very small organization. While it was a stand alone site with only 25 people, there were some corporate rules we had to follow, we were largely allowed to operate independently so we came up with all of our own standard operating procedures, all of our own policies, our own HR, it was all local to our site as long as we complied. We were able to operate that way which was fantastic.

Self-selection of Scientists

Five out eight interviewees mentioned that scientists self-select into biotech, big pharma, or academia. Dr. Bakker said, "Big pharma is very good for people who like to operate in a very limited space." Large pharma companies specialize employees into certain roles. This can feel limiting for enterprising people such as Dr. Bakker. Dr. Bakker felt that the big pharma company she was working with did not meet her need for innovation and creativity. In biotech, she felt comfortable to pursue more and a wider variety of projects. At her biotech, she hired people with a mindset of "roll up your sleeves and getting stuff done."

Mr. M calls some of the scientists that are attracted to biotech companies "cowboys". They are good at handling ambiguous situations, but have trouble adapting to the specialization required in big pharma. Due to the smaller number of employees in biotech companies, each employee has to take full responsibility for their own section. This responsibility is what attracted Mr. D to work at a biotech firm for his first job after university. Mr. D said, "Basically anyone that wants to take on more responsibility ...you're going to let them take it on because you're trying to grow your company as quickly as possible so the more people can do, the better." In a larger organization, you have to build credibility and slowly gain responsibility, which is not the case with a small organization.

As you can see from Graph 2, a larger number of interviewees that I spoke with moved from big pharma to biotech than the opposite direction. This small data selection shows that scientists are more likely to gravitate to biotech firms once they have established themselves with the pharmaceutical industry.

Initiative

Another point brought up in the interviews was scientists' willingness to take initiative. Dr. K mentioned that many big pharma companies have startup idea events where they encourage employees to submit ideas for a new business and then the big pharma company offers to fund them. The big pharma company usually asks for the first option on acquiring their idea once it is developed in return. Dr. K says that these events are under-utilized. He attributes it to the type of workers and scientists who work at big pharma companies. Frequently people who join large pharma companies do not want to regularly be the person making final decisions, especially without safety structures in place.

Dr. G talks about how a company at a small scale wants people to feel like they are part of the story and that they can affect the final result. If people know that they are trusted, they are motivated and willing to put their best work in. You do not have to micromanage if they are aligned with the story.

Mr. M found that "cowboy" chemists often really hated the heavy documentation necessary in larger companies. Documentation as previously mentioned is necessary in large companies, so that people are able to coordinate their work. "Cowboys" tend to be independently minded and creative so the structure of large corporations boxes them in too much.

Equity in the Venture

Scientists who founded or joined a biotech company early are given equity to compensate for the higher salaries they would have received doing similar work at a pharmaceutical company. Equity changes the financial incentives quite significantly because it gives scientists a way to prove the significance of their work and to be compensated for the risks they took by joining a biotech firm. Dr. M says that the chance to be differentially rewarded for success is the number one thing missing in pharmaceutical companies today (Dr. M, Personal communication, 2021). Dr. C cited this as a major factor in them choosing to start their own biotech company (Dr. C, Personal Communication, 2021). If a scientist discovers a new pharmaceutical while working at a pharmaceutical company, he does not receive any reward other than a small pay bump or promotion.

Financial Challenges

All of the people that were interviewed brought up liquidity issues as a major issue for biotech companies. As noted by Drs. G and C, financial liquidity problems are common early in a biotech company's lifecycle. According to Dr. G, booms in a field can make the process of finding money relatively easy to obtain from investors. If a field is not in an area of popular interest, acquiring funding can be very challenging.

The biotech founder, Dr. C, could recall several times when research had to be slowed down because they had run out of money. They find funding acquisition less challenging now because they have progressed their program to the point they have proven themselves from previous successes.

"It is the same process every small biotech is going through. (It was) challenging to find money. Of course you slow down a bit, but I would say overall it was quite manageable, during those times of trial. I would not say it in a major way impacts the company," said Dr. Bakker. Additionally Dr. Bakker remarked that biotech needs risk-resistant investors to invest in truly groundbreaking ideas. Currently, big pharma is too risk-averse to fund risky, but necessary, drug ideas. Traditional investing has too short of an investment window and a fear of risk that is discontinuous with the statistical chance of failure.

The investors seem to be making some changes though. Dr. Bakker noted that if you look at the investment world now compared to a few years ago you will see that a couple of research foundations that started to invest in research and it was called venture philanthropy is investing in risk, the kind where you invest in a worthwhile cause and then you hope that it works. Now a lot

of foundations are investing with this venture philanthropy but with the wrong mentality. They are already thinking about the money that is going to come back. And that of course is the wrong way to think about it because you don't invest in risk. "So I think we need to revisit the whole risky investments because I think the only way to discover new things efficiently is by investing in risk. We need to recreate the risky investors," stated Dr. Bakker.

Flexibility

Flexibility was an issue that had divided views amongst those I interviewed. Most felt that flexibility can be a big advantage for biotech companies over larger pharmaceutical companies. Biotechs are able to pivot which direction they invest in without having to consider their existing portfolio or major changes in the corporate structures. Biotechs' nimbleness allows them to follow the science wherever it leads. Dr. C and her partner for example are able to make very quick decisions because their decisions do not have to go through many committees. Having an equity stake as well makes decisions much more personally motivating.

Mr. D argued that small biotech companies have to pivot because they are focused on a single product, so all of their attention is focused on that one market segment. Companies with a larger portfolio likely are diversified and their focus is split between all those projects. Necessity is the mother of invention. Dr. K agreed that biotech companies continue to develop because they are very nimble and have a culture that wants to prove their worth.

The flexibility of small biotech companies proves to be a deciding point in their efficacy in the early stages. As previously discussed, companies look through thousands of potential APIs before settling on a dozen or so APIs to begin to do preclinical research on. In preclinical research, the company has to be able to make quick decisions on which path to follow. In the early stages of development, companies are able to play around with the formulation and even the dosage to figure out what is most efficient. The flexibility of small biotech companies proves to be a deciding point in their efficacy in the early stages.

Both Dr. K and Mr. D explained in their interviews, small companies have a much looser organizational chart, and have much broader roles. A lower headcount means that ideas can be dispersed much more organically. For example, you might run into the chief scientific officer during lunch and just have a conversation about a new idea. The broader roles increase the bench strength of the organization because employees are not nearly as specialized, which leads to them using a broader range of their skills more frequently and being able to substitute for other members of the team more easily than if they were working in a large pharmaceutical company. Within the early stages, this can be very valuable because each employee has personal experience with a large selection of the process. From having a more complete picture of what is happening, employees can make informed suggestions about ways to improve the process or catch mistakes that are caused by different steps interacting.

Biotech companies by necessity have to be flexible. They don't have enough money to support multiple projects simultaneously. If a project were to fail in a large pharmaceutical company, they could simply write-off the project and move team members to different projects. Biotech companies have to redirect their existing research into a new project because they have

no other option. The first biotech Mr. D worked with had to redirect their technology and research away from food additives to pharmaceutical projects because their company had only enough money to do one project well.

Flexibility is also useful during periods of disruption because subconscious biases toward path dependence and hence fear of cannibalizing existing products may not be present in biotech firms because they have far fewer products in the market to protect. Mrs. L believes that "large pharma companies are going to have to adapt several additional changes to be dynamic in the future. There are a lot of major shifts in healthcare coming from technology and socio-economic factors. "Are we going to continue to allow epi-pens to be hundreds of dollars or for diabetic treatments to be so expensive?" These disruptions could disrupt existing business models built on blockbuster drugs and lead to a more advantageous market for biotech companies hoping to be acquired.

Mrs. L offered a dissenting opinion. She said that if you structure your matrix organization well, decisions can be made quickly because it is very clear who has, and more importantly, who does not have, the authority to make decisions. She has seen large organizations offer more flexibility than small ones because they have specialists that can help pivot and the money to change paths more readily.

Reliability

A large benefit that was mentioned by participants of the interviews is that large pharmaceutical companies are able to have very predictable results. Dr. K argues that large pharmaceutical companies come in when the process needs to become really regimented. "The major pharmaceutical companies should act as a mother ship and come when rigidity is needed." (At Phase III) That doesn't mean that they can't have some further adjustments at that point, but you're not making large changes to the overall process, your reagents, your root of synthesis is pretty much fixed at that point." Mr. M also agreed when he said that the documentation necessary to get regulatory approval gets very dense as you near the end of clinical trials.

Purity

The purity of the pharmaceutical product can be a major advantage for pharmaceutical companies who have experience providing a product with high purity. Dr. K says that large companies have very exacting levels of quality,which is very valuable for producing at scale. As Mr. D mentioned, the process for making an API at 10 kilograms and at 10 grams can be, and often is, completely different. Mr. D says that one of the advantages for large pharmaceutical companies is that they have long-standing experience getting products scalable and at a high purity level." This is really important because you do not want to create any toxins especially when you are producing at scale.

Dr. G briefly mentioned that size brings with it much more stable and reliable expectations. "He does note that it would be a massive undertaking for a small biotech to scale up

enough to bring a product to market. The commercialization process requires a large marketing team and infrastructure that is not easily available.

Dr.M mentioned that this is becoming less of an issue for biotech companies because many companies known for their generic products are building additional business units and facilities to produce pharmaceuticals at scale. These generic companies also have experience producing drugs at full scale. So this barrier is becoming easier to circumvent for biotech companies that want to scale up their company.

Summary

In this section, quotes were extracted from interviews and then associated with the concepts that underlie their topics. This data will prove essential in the discussion section as they are combined with the material in the literature review as well as new literature. While there were disagreements amongst the interviewees about the efficiency of pharmaceutical companies, there was wide agreement about the primary weakness of biotech companies being related to their capital shortages.

Discussion

Research Questions

1. **What stages of the pharmaceutical development process are biotech companies best fit to handle?**

   Based on the shared views of participants who were interviewed in this study, small biotech companies are best able to handle the early stages of pharmaceutical development because of three reasons: flexibility, equity in the venture and self-selection of scientists.

2. **What stages of the pharmaceutical development process are large pharmaceutical companies best fit to handle?**

   The study revealed that large companies are best structured to take over in the later stages of pharmaceutical development due to two major factors: reliability and financial strength.

The two components, novelty and impact, that underlie the definition of disruptive innovation are split within the Pharmaceutical field. Biotech companies are really good at creating novel ideas. But, the impact is exerted through the large pharma companies because they have the resources and expertise to navigate the regulatory process. This dichotomy in the past has made it hard for researchers to compare their results. The ecosystem of the pharmaceutical world keeps changing as access to capital and new technologies come along. Like any ecosystem, the balance point between two populations will vary based on the conditions around it. But based on my interviews, I posit that Pharmaceutical companies' advantages begin to become predominant towards the end of phase I trials and enter full force during phase II trials. This is shown from my

interviews where none of my participants, who were involved in big pharma, were aware of an API that originated in a big pharma company. Dr. M even went so far as to say that big pharma companies no longer have the capacity to originate an API except a vaccine candidate. There is an intuitive logic to this approach as well because pharmaceutical companies do not have to carry any losses on APIs that failed in preclinical trials. The pharmaceutical company just waits for an attractive API to be developed and awards the successful startup or biotech company with a premium for their success.

Why Biotechs are Efficient in the Early Stages

Flexibility

When a moment of crisis comes and people are put into a negative mood, people acting in those situations make more data-driven decisions and avoid established approaches (Gasper, 2003).

Cooperation with other companies

These connections can help new entrants overcome the incumbent advantage of developed professional relationships. mentioned in Obal's 2013 paper. For startups without existing relationships, developing connections can be a big hurdle to overcome.

This makes sense given the large costs of conducting preclinical testing (Michelson et al., 2019; Perrin, 2014). This matches the funding challenges described in the literature review (Waagø, 2004; Janney and Folta, 2003).

Equity in the venture Some literature has found a correlation between stock options and firm success in the broad market (Athar,2020). Jones et al. pulls from a ten year study of Finnish businesses to show that stock options have negligible effect on performance for Finnish companies (2010). Jones et.al argues that many of the studies that depict positive performance results from introducing broad stock options are based in either the United States or United Kingdom (2010). Based on a study of companies from the Korean Stock Exchange, Profit Sharing Plans (PSPs) and Team Incentive Plans (TIPs) have a positive correlation with productivity while stock option plans do not (Kato, 2010). A recent meta-analysis of the effectiveness of profit-sharing on productivity, that included a wide selection of developing economies in addition to developed economies, found a positive correlation between profit sharing and productivity with 58% of surveys examined finding positive statistically significant productivity effects at 10% percent confidence level (Doucoglias et al., 2020).

An additional element that warrants further discussion is if possessing stock options helps internalize a firm's struggle between tackling the most interesting scientific problems and the financial needs of the firm. Profit is like oxygen for the firm; it is essential, but it is not the sole goal of the firm. Dr. K believes that large pharma companies need to divest from originating Active Pharmaceutical Ingredients and let biotechs do what they are good at. For this to succeed, it is necessary for the founders to have a sense of ownership in their idea during the early stages of development because it is completely unproven at that point. That sense of ownership is tough to foster in a large pharma company where credit for patents is widely distributed and your effort makes it impossible to determine change to the bottom line.

Self-selection of scientists

One of the most interesting ideas brought forward by my interviewees is that scientists self-select into a biotech or pharmaceutical company. Dr.Bakker said Big pharma is very good for people who like to operate in a very limited space. She felt somewhat imprisoned while she was working at big pharma, because people are given one role to do and there is a feeling that your career path is locked. This locked career path didn't meet her need for innovation and creativity."In biotech you don't have that luxury, so you really need to hire people with a different mindset. People with a mindset of roll up your sleeves and get [expletive] done. That is in fact what you need in a biotech." . The biotech he joined allowed him to do a wide multitude of tasks and to make a measurable impact. If biotech engages scientists more interested in independence and creativity, it would be a boon for biotech companies in the early stages of development. The reverse would be true as well because Pharmaceutical companies would attract people that enjoy structure and well-defined research activities which would be beneficial in later pharmaceutical stages. What highlighted this difference was when Dr. K was asked about whether the major pharma company he had previously worked for had a program where employees could submit ideas for potential spinoff ideas. He responded that this major pharma company as well as the other pharma companies he had worked with had spinoff programs, but participation rates were very low. He accounted for this difference to the type of people that are likely to apply to work at major pharmaceutical companies.

As mentioned in the literature review, star scientists can prove to be major contributors to any team they find themselves in. As Zucker and Darby mention in their 1996 article, small biotech seems to receive the lion's share of star scientists. This could be because the flexibility of the biotech environment allows the star scientist the ability to try out several ideas and get a fully fleshed out idea of a problem.

Knowledge siloing: The interviews confirmed that knowledge siloing is a phenomenon that occurs within larger companies. Within the early stages of pharmaceutical development, more flexibility is needed to adjust dosages and to decide which API is the most promising to pursue. As Waal and his colleagues noted knowledge siloing significantly harms organizational flexibility because relevant information is being withheld.(2019)

Why Big Pharma is More Efficient in Later Stages

Organizational Complexity

The theme of organizational complexity interplays significantly with factors from the literature review such as specialization, potential product cannibalization, Organizational inertia and delay & misallocation. Organizational complexity allows for companies to employ specialists to get very good at a certain tasks. As Dr.Bakker pointed out this specialization can lead to an unhealthy point where employees do not have a wider understanding of the value of their contribution to the whole organization and prevents those accidental moments of inspiration

because people are focused on one part of the chain. Mrs.L's perspective on properly structuring the organizational chart opens up the possibility that people's contributions to the organization can be recognized which is important to keeping scientists happy(Lam,2011) With addition of more complexity, it adds additional departments that all need to coordinate which is likely to slow down their response time(Hannan et al.,2002). This resistance to change also creates an environment with fewer changes which allows for the slow methodical method that is needed to complete the documentation necessary to satisfy the requirements of the FDA and EMA.

Reliability

As pharmaceutical development reaches phase II, reliability begins to become essential for success. In phase two, the quantity of drugs to be delivered significantly increases. Dr. K, Dr. G and Mr. D asserted based on their experience in the industry that the process of creating a drug is different for each phase of development. What worked at a few grams has to be changed to be more affordable and scalable. At early stages such as the preclinical stage and phase I, the drug is made in small batches at a scale small enough for each pill or dose to be inspected.

As Mr. D said, ten kilograms is the rule of thumb where a company can be sure that their idea is scalable enough to make it into the customer's hands. This tipping point benefits established incumbent companies who have access to expensive machinery that is affordable at scale but is too large of an investment for a small biotech. Since incumbent companies have multiple product lines, they can spread the investment costs of sophisticated machinery amongst all of their product lines. The slow aspects of bureaucracy keep mistakes from being incorporated into the final product and provide several layers of redundancy. Each member of a team in a large incumbent has a narrow focus and is able to do their task at a precise level (A. Bakker, Personal communication, 2021). All employees, in large incumbent companies, need to know how to properly fulfill their section of the process. All members with decision making talent have earned respect from their coworkers by working their way through the hierarchical structures of the firm. At these later stages, a CEO or manager wants everything to be unexciting and predictable. This is essential because at scale mistakes are replicated into a whole batch. Even more importantly those mistakes are given to many more people and a more general section of the population with less serious diseases (FDA, 2014).

If the process is not predictable, the results on whether the product will be an effective treatment will be tainted. Phase II is when the product's therapeutic effects are being measured (FDA, 2014; Wong et al., 2014). For the therapeutic effects to be properly measured, the dosage must be accurate and free of contaminants, which can potentially counteract the API or cause unintentional effects (Yin, 2012). In order for a drug to be approved by regulatory bodies, scientists have to be able to prove that the API was the cause of the change in the subjects' health. A botched phase II trial can directly cost between 7 and 19.6 million dollars as well as opening the company up to lawsuits (Wong et al., 2014).

In Phase III, the need for predictability is even stronger. The Federal Drug Agency and European Medical Agency want at phase three for the company to be running clinical trials to provide details on their processes for creating the drug as well as the inactive ingredients that will be delivering the API (Mr. D, Personal Communications, 2021). Deviations in the processes or inactive ingredients are seen by regulatory authorities as suspicious or could throw the New Drug

Application approval into question. (Mr. D, Personal Communication, 2021). A potential impurity at this stage could harm thousands of people. A bad batch could invalidate the results of any medical trials conducted at that time until the source of the impurity is found. Each failed medical trial can lead to a loss of up to 52.9 million dollars (Wong et al., 2014). A bad trial can lead to the FDA giving the new medication a very narrow population that they can advertise to. An imagined scenario would be a diabetes medicine with a good label that is able to be used for all type-2 diabetics while a diabetes medicine with a bad label can only sell to type-2 diabetics under thirty with no existing heart issues.

In addition to the regulatory agencies, pharma companies have to convince insurance companies of the efficacy of their medications compared to other treatments(Kaitlin,2010). Insurance agencies determine whether a new medication will be fully covered (Mrs. L, Personal Communication, 2021). If a medication is considered too risky, insurance companies can push their clients to follow existing standards of care options before trying a new medication (Mrs. L, Personal Communication, 2021).This second barrier of entry can make any medication unprofitable even if they pass through clinical trials.

Relationship with Regulatory Agencies

The relationship with regulatory agencies mentioned in the literature review was at least partially explained by the frequent hiring of former FDA/EMA employees by large pharmaceutical companies. The migration of FDA employees to biotech companies can potentially be explained by scientists with a preference for process or stability being attracted to large pharmaceutical companies. The FDA is highly process oriented because their purpose is to ensure that clinical trials are effective and have thorough documentation showing any potential effects of the pharmaceutical.

Financial Strength

The factors from the literature review of enormous capital requirements, failure absorption and threat of acquisition are deeply connected to the financial challenges mentioned in the interviews.

As previously mentioned in this paper several times, developing a pharmaceutical is extremely costly. Everyone of my interviewees touched on the financial challenges that biotech companies face as well as pharmaceutical companies. The financial power of large pharmaceutical companies kept emerging in interviews as their dominant advantage.In 2010,The top fifteen pharmaceutical firms held ninety percent of the capitalization in the industry (Giaccotto, 2011). For biotech companies to get access to capital, they could either partner with pharmaceutical companies, who understand their industry or face a high interest rate from more traditional investors (Giacotto, 2011). In most situations, pharmaceutical companies could create validation for the biotech's idea by acquiring them (Humphrey-Jenner, 2014) or another investment arrangement such as receiving first right of refusal for the biotech's idea (Mr.M, Personal communication, 2021).

Biotech companies have some other ways to at least pay for Preclinical trials which are somewhat inexpensive. For example, a Systematic Literature Review (SLR) which looks at existing academic literature to determine if a drug is promising is estimated to cost around $141,000 (Michelson et al., 2019). Additionally, mice trials are estimated to cost roughly $330,000 to conduct properly (Perrin, 2014). For example, nonprofits such as the Children's Tumor Foundation will provide investments for drug candidates that match charities' goals (Dr. Bakker, Personal Communication, 2021). Insurance companies will also take a minority investment in a biotech or medical device if it offers a significantly more cost effective option to existing treatments (Mrs. L, Personal Communication, 2020) Funding for the initial stages can also be dependent on if there is any hype or excitement in the news around your field. If you are fortunate, your field of specialty or technology might experience a boom in the market. Dr. K and Mr. D's biotech companies were both recipients of booms in the market, which made their respective firm's entry into the market significantly smoother because angel investors were entering the market.

These financial challenges are not necessarily a death sentence for biotech companies. The book *Great by Choice* suggests using several small "bullets" to test multiple ideas before making a strategic decision to fully invest in one API (Collins and Hansen, 2011). Collins and Hansen specifically draw from Amgen as an example of a biotech company that started with a modest budget of $100,000, used this approach, and was able to scale up and compete with Genentech. A Lot of companies that were once small biotech companies are sizing up becoming giants in their own. Vertex which at one moment was a scrappy biotech company has matured and is now following in the footsteps of big pharma companies.

Recommendations and Implications for Theory, Research, and Practice

Based on the initial research conducted by this thesis, pharmaceutical companies should specialize even more into late stage development because that is where their natural strengths lie and small biotech should remain flexible. A principle that should be applied here is that general knowledge should never be a substitute for the specific circumstances of a company. Companies are complex organizations with features beyond just their number of employees or capitalization. Many of the factors mentioned in this paper are inclinations or predispositions that companies are more likely to fall into. A company's corporate culture and environment can counteract or enhance these predispositions.

Each company is made up of independent actors making decisions that shape the aggregate results. Dr. K advises all of the biotech companies he consults with to stay virtual for as long as possible and avoid acquiring major infrastructure until necessary. Additionally, many biotech companies could feasibly increase their complexity if they could gain access to more capital. Traditional investors don't have a good model or method for investing in biotech companies. As we have seen from the Covid-19 pandemic, it is impossible to increase the speed of clinical development even when you have all of the world's resources at your fingertips. This is

relatively unique to the pharmaceutical industry. In addition, pharmaceutical development takes much longer than other industries, most notably the software industry where you can have a working prototype within a month and already start receiving revenue. The issue of funding audacious ideas was at the forefront of Dr. Bakker's mind when discussing the future of the industry. This problem for biotech companies in particular seems to be much more an issue of liquidity than solvency. Many of my interviewees had anecdotes of biotech companies that had products that would be cost effective and even provide medications to untreated populations but were unable to because their companies were considered too small or their release window was too long. Dr. Bakker brought up how non-profit organizations had come in to fill this need but have become too conservative in their investing because they relied on future revenues of the product for existing costs.

Simon Sinek's Infinite Game Theory. Simon Sinek argues that companies need to shift to seeing their company and their competition with their rivals as an infinite game. If the leaders in the company see themselves in an infinite game they are just players with finite time and resources. Their legacy and even the company can continue beyond their career. I think this is especially valuable for the Pharmaceutical and Biotech industry because the problems they are taking on such as cancer and aging will likely not be won in our lifetimes.

Conclusion

The trend noted by IQVIA (2019) toward emerging biopharma companies originating and developing API's further into the process appears to be reinforced by major organizational dynamics.The most predominant advantages of pharmaceutical companies are their ability to produce pure product at scale and their ability to obtain funding. Both of these advantages do not seem to infer permanent advantages. The biggest issue for biotech was the problem of liquidity. If the banking sector were able to create an innovation to handle long term uncertainty, this problem could be overcome. Second,the issue of producing at scale is being eroded by contract manufacturers who have experience producing at scale.

Directions for future research:

One of the most interesting ideas brought forward by my interviewees is that scientists self-select into a biotech or pharmaceutical company. This could be an interesting route for a later paper to investigate. If that study found a connection between a scientist's approach to risk and their choice to enter a biotech company or a pharmaceutical, that would have strong implications on how pharmaceutical companies should approach creating spinoffs and organizational structure.

A second potential line of research would be investigating different approaches legal departments and executives can take to decrease the time spent conducting due diligence on cooperation agreements. The anecdotal evidence from Mr.M and Dr,C indicate that there might be an improper risk taking place.

Delimitations

A direction this paper could have followed, but did not was to look at scientists' motivation for creating innovation at either biotechs or pharmaceutical companies. This concept was alluded

to by two of my interviewees who said that scientists who join big pharma often do not initiate spinoffs or their own projects because they value the corporate safety net and the predictability found there. This paper also did not look at scientists that decided to research in an academic setting instead of entering the industry. An additional direction this paper could have gone is to look at biotech companies' access to investors. On the surface level, biotech seems to require a very different kind of investor then what a typical venture capital firm (VC) or company can offer.

Limitations of the Study

COVID-19 led to a dramatic shift in capital investment. Beyond the personal challenges, many managers in the biotech and pharmaceutical field were hard to reach or interview. Vaccine development, which had been an unexciting field to invest in, was thrust into the limelight. This shift in funding meant that many companies outside of vaccine development spiraled into financial trouble or had to make large structural changes to their business model. This led to a smaller selection of possible interview subjects. Additionally, all but one interview subject requested anonymity due to increased media attention on the pharmaceutical field.

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