Risk, Regulation and Strategy: A Multi-Case Study of the Botanical Drug Industry

_____

Benjamin William Lewis

30th April 2022

_____

A Thesis Submitted in Partial Fulfilment
of the Requirements for the Degree of
Master of Bioscience Enterprise.

The University of Auckland, 2022.

Abstract

Regulation is a necessary part of life sciences as it ensures product quality and patient safety. The Food and Drug Administration (FDA) is the regulatory agency which facilitates patient safety by ensuring quality and efficacy of all drugs which are on the market in the US. The FDA botanical drug development pathway is a relatively new route to market offered to firms developing botanical-based polymolecular drugs. With only three approved botanical drugs to date, this market is still in its infancy. Achieving FDA approval for a botanical drug is a rigorous capital-intensive activity, but without approval these products cannot be sold on the US market.

Effective development strategies and risk mitigation techniques are important to any firm aiming to achieve regulatory success. There has however, been no research into development strategies and risk mitigation techniques for firms attempting to gain FDA approval for botanical drugs. Therefore, firms have little guidance to make effective decisions when developing their botanical drug candidates. There is rapidly growing global interest in the use of botanicals for human health, as botanicals are largely seen by consumers as 'safer' alternatives to conventional synthetic medicines. Therefore, this is an important area of research to facilitate market access and broader accessibility of botanical drugs to consumers.

The purpose of this thesis is to gain insight into the major regulatory challenges faced by firms developing botanical drugs and understand how firms strategize and minimise risk when working towards FDA market approval. An exploratory qualitative research approach employing a multiple case study method was used to inspect these phenomenon. Purposive sampling and company benchmarking was used to identify cases, which were then built using in-depth semi-structured interviews and multiple secondary data sources. Three cases were built, each based on an international botanical drug development firm, who, at the time of writing had a different regulatory outcome: failed, on-going and approved.

Through thematic analysis of the study data, this study identified nine important findings to inform firms of the major challenges faced when developing a botanical drug through the FDA approval process. These challenges majorly occured in the early stages of botanical drug development and included challenges in preclinical studies, lack of clarity on usage of previous human use data, communication with the FDA, financing the development process, management structures within the firm, strategic

decisions on collaboration, choosing the indication, choosing the right development strategies and the right partners to mitigate risk.

The challenges exposed in this study, triangulated with existing information from the literature, allowed for practical recommendations to firms developing botanical drugs and aiming for FDA approval. The overall recommendations to these firms focused around decisions that firms could take to improve regulatory success, particularly in early communication with regulators, strategic collaborations, aligning the firm management structure and using risk mitigation tools.

Acknowledgement

First, I would like to say thank you to my academic supervisor, Alex Sims. I appreciate all the support and guidance she has given me throughout my research. Without her, this thesis would not have been possible.

Secondly, I would like to express my gratitude towards my industry supervisor Margot Bethell, Andrew Kelly, and the team at BioPacific Partners. Without your ongoing support and insights, I would have been lost on this topic.

I would also like to thank my family for supporting me, especially over the final few weeks before submission.

To Zeus, without you at my side every day I think I would have lost my mind. Thank you for being my best mate, always being there for me, and being a good boy.

Finally, I would like thank Deanna. Words cannot describe how thankful I am for you being in my life and always being happy to help me with anything, without your daily support there is no way this would have been possible.

Table of contents

List of Figures

List of Tables

Chapter 1: Introduction

This chapter provides an explanation on the purpose of this research. This research has been conducted to expand the literature and develop an understanding of the novel botanical drug development pathway offered by the United States Food and Drug Administration (FDA). The aim is to uncover the key regulatory challenges faced by firms developing botanical drug candidates and understand how firms strategize to satisfy the FDA regulatory requirements.

1.1 Background

Botanical health products have been used in human health for millennia and typically have high public acceptance for their proposed therapeutic effects (Razzaghi-Abyaneh et al., 2012). The FDA is the regulatory body who governs the regulations of foods, drugs and medical devices in the United States of America. There have been very few approved botanical products as drugs by the FDA, due to a lack of meaningful scientific data and a well-defined regulatory path of approval. There has recently been a resurgence in the use of botanical products by consumers for their believed preventative and curative properties, which are based purely on anecdotal evidence (S. Y. Pan et al., 2014). Therefore, it is important that consumers who wish to choose plant-based 'natural' medicines have access to products which have been tried and proven effective.

In 2004, the FDA released the Botanical Drug Development Guidance for Industry (BDDGI) draft document which offers advice to firms who are developing botanical drugs. Botanical drugs are unpurified, unmodified and contain ingredients from a plant, algae, macroscopic fungi, or combination thereof (FDA et al., 2016). Botanical drugs are sold and regulated on the US market as pharmaceutical products. While botanical products, which are commonly used for their perceived health benefits, are sold and regulated as foods.

Drug development is a time and capital-intensive activity. The average cost of developing a conventional small molecule drug for market is around $1.3 billion US (Wouters et al., 2020). The FDA subjects botanical drug applications to the same level of scrutiny as conventional small molecule drugs (Hoffman, 2015). However, given the botanicals' chemical and biological complexities, the struggles in characterising their pharmacology, therapeutic efficacy and consistency remain a regulatory challenge

(Wu et al., 2020). To date, only three botanical drug products have been approved. The first was Veregen, an ointment approved in 2006 used to treat perianal warts. Second, Mytesi, an oral tablet approved in 2012 for the treatment of drug-induced diarrhoea from HIV/AIDS medication. And third, Epidiolex, an oral CBD spray approved in 2018 for the treatment of seizures in children.

The botanical drug market in the US is expected to grow, as the number of investigational new drug (IND) applications submitted to the FDA have increased significantly since the release of the revised BDDGI document in 2016. However, due to the small number of applicants that have successfully made it to market, there is little literature on successful firm strategies in the botanical drug space.

Strategy and risk mitigation are both important elements of firm management. Engaging in strategic planning can provide direction to a firm and align key stakeholders to produce long term meaningful results like successfully achieving regulatory approval of a botanical drug product (Seimetz, 2017). While risk mitigation is about enabling the firm strategy to function optimally by identifying, avoiding, and overcoming obstacles which may inhibit the firm from moving forward (R. S. Kaplan, 2009).

The botanical drug development process consists of multiple overlapping and interconnected phases, with various influencing factors. As the botanical drug industry know-how is still in infancy, other than the BDDGI recommendations provided by the FDA, there are no established best practices for botanical drug approval. With botanical drug firms experimenting in several different regulatory development strategies, there is not only a delay in the release of effective and needed therapeutics to market, but also a loss of capital being invested in innovations that are being inefficiently commercialised (Checo et al., 2019; C. Wu et al., 2020). It is vital that key regulatory challenges, such as the chemical and biological complexities described above, are identified alongside how botanical drug development firms have strategized to overcome these challenges.

1.2 Statement of the problem

Regulation is a necessary part of life sciences to ensure product quality and patient safety (Mohs & Greig, 2017). The botanical drug development process is designed to minimise risks while maximising efficacy, through various regulatory testing (Mohs & Greig, 2017). To maximise success in the various regulatory requirements, and so that firms can get their drug to market to generate revenues, it is

critical that decision makers engage in key regulatory and organisational strategies early in the development process (Seimetz, 2017).

Currently, there is an extensive amount of drug development regulation literature, strategic firm management literature, and risk management literature. There is a small established body of literature for FDA botanical drug development, however much of this literature is outdated and focuses on the regulatory challenges faced during development. The strategic management and risk mitigation literature is extensive but is generalised over several different industries. Few studies have been conducted exploring strategic management and risk mitigation in the biotechnology and pharmaceutical industry. Furthermore, there have been no identified strategic management and risk mitigation studies specific to FDA botanical drug development.

Using previous literature and case studies built on primary and secondary data sources, this research attempts to provide an update to the already established botanical drug development literature. Furthermore, this research will be the first of its kind to look at firm strategy and risk management in the context of the FDA botanical drug development space.

1.3 Purpose and significance of the study

The purpose of this research is to explore the regulatory challenges, strategies and risk mitigation techniques used by firms who are developing botanical drug candidates via the FDA botanical drug development pathway. The research findings can be used to generate recommendations for firms who are looking to develop botanical drugs for the US market. These recommendations will identify where most regulatory challenges are faced during botanical drug development, with suggestions on how to mitigate these challenges. Based on the case study data, comments and recommendations on strategies and risk mitigation techniques will also be made.

1.4 Research question and methodology

This research will investigate:

> *What are the major regulatory challenges faced by firms during botanical drug development, and how do firms strategize to satisfy regulations when attempting to gain FDA market approval?*

To investigate the above question, three sub-questions are addressed throughout the research and data collection:

1. *What are the major regulatory challenges in botanical drug development?*
2. *How do firms strategize to satisfy the FDA regulatory requirements, and specifically, how do the major regulatory challenges identified in this thesis influence or alter how firms strategize during botanical drug development?*
3. *How do firms minimise risk during botanical drug development, and specifically, how do firms minimise risk associated with these major challenges?*

To answer the above sub-questions, an inductive exploratory qualitative research approach with a multiple case study methodology was used. Three cases were generated, each of which with a different current regulatory outcome: failed, ongoing and approved. This enabled comparison of outcomes and an understanding of the differences between each case that contributed to their regulatory outcome.

This research was conducted in several steps. First, the context and the purpose of the research was identified. Second, a literature review and the methods of approach were developed. Third, a company benchmarking list was created, which facilitated outreach and recruitment to firms for semi-structured, in-depth interviews. Fourth, secondary data was collected to generate cases for firms who responded to the outreach. Fifth, all data sources were coded and analysed, followed by the generation of case studies through triangulation of data. Finally, case studies were analysed and compared, allowing recommendations to be generated from the research data.

1.5 Thesis structure

The structure of this thesis is outlined as follows:

Chapter 1 is the introduction to the research and illustrates the topic and significance of what this study aims to achieve. Chapter 2 provides context and important background information on the research topic. Here, the FDA and the botanical drug development industry are also introduced. Chapter 3 discusses the strategic management and risk mitigation literature, highlights key regulation literature, and discusses the botanical drug regulation challenges. Chapter 4 provides a description of the approaches taken in this research and the data population, collection, and analysis methods. Chapter 5 presents the results obtained from the collected data. Here, individual case data is presented and discussed, followed by cross-case analysis. Chapter 6 discusses the results obtained in context of the identified themes within the data, and prior literature. Limitations and strength of this research are also discussed here. Chapter 7 concludes the study findings and provides recommendations for firms and future botanical drug future research.

Chapter 2: Research Topic Context

This chapter will cover the following factors surrounding botanicals: historical overview, current trends and challenges surrounding botanical products, an introduction drug development and how botanical drugs are regulated by the FDA. It is important to have an understanding of the history and modern day use of botanicals to understand this study in light of botanical drug development challenges and firm strategy.

2.1 Botanicals; Botanical products and botanical drugs

'Botanicals' are defined as the ingredients or finished products of a substance relating to a plant, or a substance obtained from a plant (Tamayo & Hoffman, 2017). Depending on the botanicals' intended use and the region in which they are to be marketed, they can be regulated as foods, dietary supplements, drugs, devices, cosmetics, colour additives, fragrances flavourings, traditional medicines, complementary medicines and more (Bilia & Costa, 2021; FDA et al., 2016; Thakkar et al., 2020; C. Wu et al., 2020). Botanicals may exist as single plant-derived compounds such as *Ginseng*, traditionally used to boost immunity, energy levels and reduce inflammation (Zhou et al, 2016). Botanicals may also exist as complex mixtures of botanical components from one or more plant, such as *Salvia miltiorrhiza* and *Pueraria lobate* used in traditional Chinese medicine for the treatment of coronary heart disease (Zhou et al., 2016). For the purpose of this research, the term 'botanicals' is the broad term that will refer to substances that are obtained from a plant and turned into a variety of different end products. 'Botanical products' will refer to botanicals that are regulated and sold as foods, cosmetics and dietary supplements, while 'botanical drugs' will refer to botanicals that are regulated and sold as pharmaceuticals.

It is important to make an early distinction between botanical products and botanical drugs. Botanical products, also termed natural health products, complementary medicine, phytomedicine or phytotherapy, refers to the plant, plant materials, plant preparations and finished plant products that contain part of a plant or other materials as active ingredients (Pan et al., 2014). The plant parts that are used in botanical products include algae, seeds, berries, roots, leaves, fruit, bark, flowers, and even the whole plants (Pan et al., 2014). Botanical products are typically regulated as foods, dietary supplements, and cosmetics. These regulations disqualify botanical products from making labelling claims about treatment of diseases and health conditions (Nwoko & Drew, 2018).

The FDA defines regulation of botanicals based on four dictating characteristics of the product: the form/formulation of the product, the route of administration (topically, orally, or intravenously), the safety and the intended use of the product (Tamayo & Hoffman, 2017). For example, a botanical developed to be applied topically, can never be sold as a food or dietary supplement; however, based on the botanical's intended use, efficacy, and safety profiles, it may be marketed as a cosmetic, medical device or even a topical drug (Nwoko & Drew, 2018).

Botanical drugs, like botanical products, are a finished labelled product that contain ingredients from a plant, algae, macroscopic fungi, or combination thereof (FDA et al., 2016). Although they have distinct differences. A botanical drug is a refined botanical product which is intended for use in diagnosis, curing, mitigation, treatment and/or prevention of disease in humans and is formulated as a solution, powder, tablet, capsule, syrup, elixir, topical or injection (FDA et al., 2016). Botanical drugs must undergo strenuous preclinical and clinical testing and are held to the same regulatory standards as other drug products (Lee, 2015). However, botanical drugs often have unique features which differentiate them into their own category, such as a lack of a single distinct active ingredient, complex mixtures, and often substantial prior human use (FDA et al., 2016). Furthermore, the Centre for Drug Evaluation and Research (CDER) states that fermented and highly purified or chemically modified botanical substances are not considered botanical drugs (FDA et al., 2016).

2.1.1 Botanicals: A historical perspective

Humans have used plants and other natural compounds as medicines to treat a wide range of ailments for thousands of years (Pan et al., 2014). The history of using plants and other naturally sourced compounds for medicinal use dates to ancient times across various regions such as China, Egypt, Greece, India, and the Middle East (Knoess & Wiesner, 2019). Archaeological studies have suggested that humans first started using plants as healing agents around 60,000 years ago, in what is now present-day Iraq (Pan et al., 2014; Razzaghi-Abyaneh et al., 2012). The oldest *documented* records of medicinal plants' usage dates back around 5,000 years to the Sumerians, who described drug preparations referring to various medicinal plants such as poppy, henbane and mandrake (Petrovska, 2012).

Initially, therapeutic plant use may have been instinctive, as is the case with animals; since at the time there would have been insufficient information to address the reasons for illness and why a specific botanical could be used as treatment (Petrovska, 2012). In time, the usage of specific compounds to treat ailments was understood and thus the traditional empirical framework of medicinal plants was gradually abandoned and replaced by a framework based on explicatory facts (Petrovska, 2012). With the advent of conventional medicine in more recent human history, botanicals in the form of traditional medicines have been challenged due to the lack of scientific evidence, despite their long standing traditional use (Marcus & Grollman, 2016).

Modern medicine has seen significant advances because of centuries of innovation and research. Yet pharmacological properties of many botanicals and animal-derived medications and minerals are still used as starting points for early-phase drug discovery and development programs (Schmidt et al., 2007). The practical use of traditional medicines, especially in non-Western cultures has resulted in further investigations of plants as new drug candidates. Some of these have led to the isolation and derivatives of naturally occurring molecules that have become well known pharmaceuticals (i.e., digoxin, paclitaxel and artemisinin drugs) (Wu et al., 2020).

2.1.2 Botanicals: Current trends and challenges

The use of botanicals for health purposes has increased in popularity in both developed and developing countries (Laelago, 2018). Furthermore, this use of botanicals is currently the primary form of healthcare for 65-85% of the world's population (Laelago, 2018). Botanicals have defied regulatory harmonisation globally, as the regulatory consensus for the use of botanicals to treat health conditions differs by country, even within shared geographical regions (Bilia & Costa, 2021; Tamayo & Hoffman, 2017; Thakkar et al., 2020). Unlike many regulatory systems, the FDA has no traditional or herbal medicines category and botanicals are mainly marketed in the form of conventional food (vegetables and spices etc), dietary supplements, or foods for special dietary use (Tamayo & Hoffman, 2017).

In recent years, there has been a resurgence in the use and interest of health oriented botanicals for various reasons (Pan et al., 2014). These reasons include the harsh side effects of single molecule drugs, dissatisfaction with treatment outcomes for chronic diseases, microbial resistances, and the high costs of many medicines (Pan et al., 2014; Pan et al., 2010). Part of the growth in the health-related use of

botanicals has been attributed to the internet and social media, where individuals flock to discuss and push the virtues of plant-based 'natural' medicines (which are largely based on anecdotal evidence) (Alotiby, 2021; Jeong et al., 2012; Pan et al., 2014). Moreover, biotechnology and pharmaceutical firms have recently begun to recognise and rediscover botanicals as a potential source for new drug candidates, particularly in network pharmacology, reflected by a renewal of strategies in favour of natural drug development and discovery (Atanasov et al., 2021; Pan et al., 2014; Schmidt et al., 2007). This interest in botanical drugs is exacerbated by the need for pharmaceutical and biotechnology companies to fill their pipelines with new drug approvals as traditional single molecule drug development discoveries are slowing and the cost of developing new drugs is increasing (Kimko & Pinheiro, 2015).

Consumers in developed nations are attracted to botanical products as a means of 'natural', preventive or curative treatments, falsely assuming that they are safe and free from side effects (Checo et al., 2019). This belief that botanical products are safe based primarily on their long history of use, is no longer tenable in view of extensive documentation of the adverse effects of different botanical compounds on human health (Marcus & Grollman, 2016). Increases in the use of botanical products may also be linked to an overall change in values and beliefs, as individuals are recognising the importance of taking responsibility for their own health (van Wyk, 2005). Which is closely tied to an increase in the awareness of diet, exercise, and stress management for longevity, all of which involve people changing their behaviours and lifestyles (van Wyk, 2005).

Additionally, in underdeveloped and developing countries, many people cannot afford conventional single molecule medicines, and those residing in rural areas rely primarily on botanicals provided by traditional healers for the prevention and treatment of disease (Marcus & Grollman, 2016). In such regions, often there are no specific laws and regulations for botanical practitioners and those manufacturing these products, which can lead to adverse effects on their consumers (Fatima & Nayeem, 2016). In addition, people may engage in self-treatment, resulting in harm (Fatima & Nayeem, 2016).

Examples of toxic effects from botanicals have occurred with the consumption of *Aristolochia sp.* commonly known as birthwort, pipevine, or Dutchman's pipe. *Aristolochia sp.* has been used in botanical medicinal preparations by the ancient Egyptians, Greeks, and Romans, and plays a role in traditional Chinese medicine (Marcus & Grollman, 2016). *Aristolochia sp.* contains the active compounds

known as aristolochic acids. The toxicity of aristolochic acids was discovered following an investigation into a cluster of adverse health conditions caused by a herbal weight loss product in Belgium in 1993 (Vanherweghem et al., 1993). Aristolochic acids were shown to congregate in the renal cortex where they caused aristolochic neuropathy, renal failure, interstitial tubulonephritis and carcinomas of the upper urinary tract (Marcus & Grollman, 2016). Furthermore, Taiwan has the highest incidence of upper urinary tract cancers globally, and recent studies have shown that exposure to aristolochic acids due to the usage of traditional Chinese botanical products is a major causative factor (Chen et al., 2012; Marcus & Grollman, 2016).

Many communities have failed to recognise the adverse events associated with the use of certain botanical products (Marcus & Grollman, 2016). While botanical products may not be as chemically altered as traditional synthetic drugs, which can induce a range of harsh side effects from muscle tissue wastage to death, they still have the potential to adversely affect consumers, even in regions with relatively defined regulatory controls (Checo et al., 2019). Botanical product side effects can come from adverse herb-drug interactions, or even from the toxic effects of compounds within the botanicals themselves (Fatima & Nayeem, 2016). Such a case is highlighted by the continual use of *Aristolochia*-containing traditional botanical products in Asia despite aristolochic acids now being known as potent carcinogenic compounds. While botanical products, like Aristolochia-containing products, are used globally and traditionally for their perceived health benefits, the majority have not undergone rigorous developmental processes to prove their efficacy and safety and therefore cannot be marketed as drugs in regions such as the USA (Pan et al., 2014; Thakkar et al., 2020).

Many consumers utilise botanical food and cosmetic products for their perceived health benefits; however, without clear evidence that a botanical can be used as an effective treatment, it cannot be marketed and prescribed by healthcare professionals as such. Furthermore, the use of botanical products can be risky as they are not subject to review by the FDA prior to marketing (Fatima & Nayeem, 2016). If a botanical product is to be marketed and used to diagnose, cure, mitigate or treat disease, then it is required to proceed through the same regulatory pathway as conventional drugs,where full marketing authorisation is required before marketing can be permitted (Wu et al., 2020).

2.2 FDA Drug Development

Drug discovery and development is capital and time intensive, and requires a sponsor to direct, manage and oversee all operations associated with the drug approval process (Jekunen, 2014). A sponsor is the pharmaceutical/ biotechnology firm, individual or research institution that takes the responsibility for conducting research and development to develop a new drug while cooperating with the FDA to navigate through its rigorous evaluation processes prior to marketing approval (Shimasaki, 2009b).

All new drug development (including botanical drug development) follows a common pathway as depicted in Figure 1 (Hughes et al., 2011). Basic research, often academic, leads to the identification of targets for pharmaceutical action, and is followed by ideation of a chemical drug concept to alleviate or prevent a disease process (Hughes et al., 2011; van Norman, 2016). Development of this conceptualisation is then continued through prototype design and pre-clinical investigations involving *in vitro* and *in vivo* studies (Ciociola et al., 2014; van Norman, 2016). On average the development of a new drug product from research and discovery, through to marketing approval takes around 12 years, and is estimated to cost between $1-2.6 billion US (DiMasi et al., 2016; Mohs & Greig, 2017).

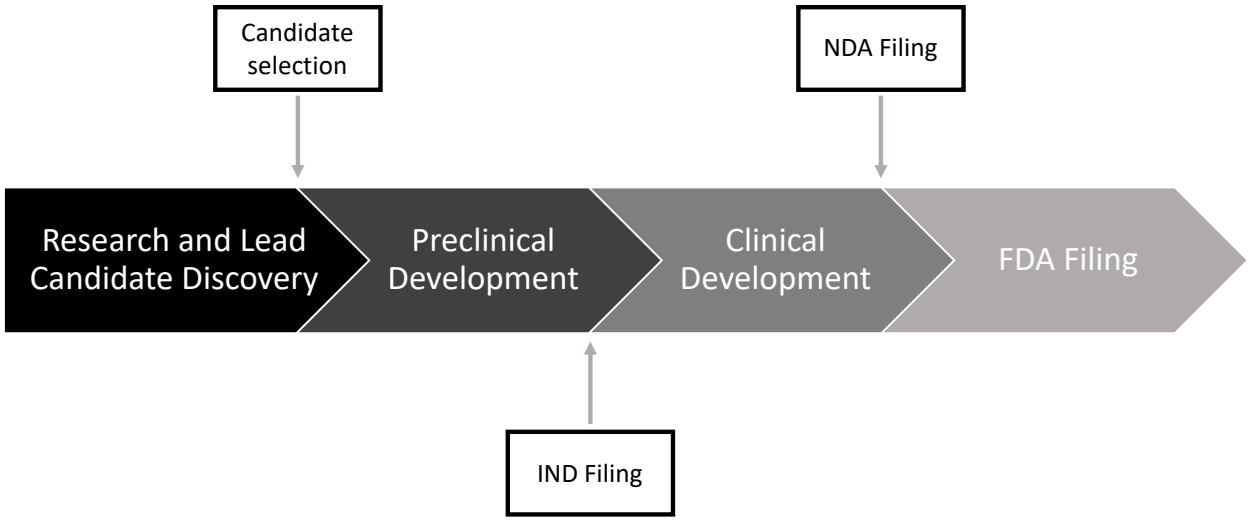

Figure 1: Simplified drug discovery and development process, adapted from Hughes et al. (2011).

Prior to drug candidates reaching the hands of any clinical researcher, a sponsor must obtain permission to start in-human clinical drug investigations by submitting an investigatory new drug (IND) application (Checo et al., 2019). The FDA encourages sponsors to meet with the FDA before submitting an IND to discuss the IND and offer help to prevent any clinical holds (refusal to allow study to proceed) from arising (Checo et al., 2019). Pre-IND (PIND) communication can provide investigators with information that will assist them in the preparation and submission of a complete IND (Checo et al., 2019; Wu et al., 2020).

After approval of the IND application, the FDA allows in-human clinical development. This stage of drug development consists of phase 0, 1, 2 and 3 clinical trials (Hughes et al., 2011). These trials are used to demonstrate the safety and efficacy of new drugs, and when concluded, result in the submission of a New Drug Application (NDA) (Hughes et al., 2011). The NDA is a comprehensive application with data summarizing all of the information from years of clinical trials and safety testing (Shimasaki, 2009b; van Norman, 2016). At the conclusion of the NDA application process, the FDA will review the NDA filing and approve, request further information, or deny the application (Shimasaki, 2009b).

There are high failure and drop-out rates in drug development with market success as low as 0.01% of all drug candidates tested (Cowlrick, 2011). The drug discovery and development process is designed to minimise possible risks while maximising efficacy (Mohs & Greig, 2017). Despite the strenuous regulatory parameters by which these products are filtered and the low success rate, the drug development process does not guarantee a supply of approved drugs which are efficacious and without risk (Abraham, 2003; Cowlrick, 2011). Candidate drugs continue to fail for a variety of reasons both in clinical trials prior to approval and for toxicity once on the market (Abraham, 2003).

2.2.1 Botanical drugs and the FDA

The development of botanical drug products within the US is regulated by the FDA in the Centre for Drug Evaluation and Research (CDER), within the Department of Health and Human Services (FDA et al., 2016; Tamayo & Hoffman, 2017). Botanical drug development, like conventional drug development, is a long and challenging process from conceptualisation through to market approval. In addition, because there are additional challenges unique to these products, the FDA offers regulatory policies that differ

from those applied to other non-botanical drugs (FDA et al., 2016; Wu et al., 2020). These challenges will be discussed later.

The FDA began to receive and review botanical drug INDs in 1984 for specified indications, and as more complex applications were received, the FDA recognised that botanical derived drug products differed from other single molecule and biological drugs (Wu et al., 2020). In 1998 the World Health Organisation (WHO) published guidelines to assist international drug regulatory authorities with developing safe and effective botanical drugs, as at the time there were too few botanicals which had known safety and efficacy information (Checo et al., 2019). With an increase in interest in botanical products as drugs, countries and governing agencies created regulations for botanical drug development. However, due to the complexity of botanical compounds and inexperience of the industry, the guidelines were difficult to follow (Checo et al., 2019).

To address the challenges associated with developing botanical drugs and to encourage and facilitate botanical based drug development, in 2004 the FDA published draft guidelines regarding the development and approval of botanical drugs (Wright, 2021). These guidelines were developed to provide a roadmap to help guide sponsors of botanical drugs (Wright, 2021). A specialist botanical review team was also created to advise and consult across multiple divisions of health on botanical drug development (Wright, 2021). In December 2016, the FDA updated and published a revised Botanical Drug Development Guidance for Industry (BDDGI), to provide recommendations intended to facilitate botanical drug development and address the unique developmental requirements associated with botanical drugs (FDA et al., 2016). BDDGI also describes the CDER's current position on the development plans for botanical drugs and advises sponsors who are interested in submitting INDs and NDAs on the application process and how complex botanical products can satisfy the FDA's drug review process. The BDDGI also states that botanical drug products are to be treated like any other new drugs, with the same level of confidence that clinical data from adequate and controlled trials with quality standards will support the NDA approval process (Wu et al., 2020). Through meetings and other communication, the FDA offers case-by-case advice to sponsors on clinical protocol design, additional studies, potential issues, and advice on the overall drug development plans (Wu et al., 2020).

To date, only three botanical drug applications; Veregen, Mytesi and Epidiolex, have progressed through the NDA stage of development and are now on market as prescription drugs (Wright, 2021; Wu et al.,

2020). Veregen (Sinecatecheins) ointment was approved in 2006 for the treatment of external perianal warts caused by the human papillomavirus. Veregen contains partially purified leaves from green tea (*Camellia sinensis*) and was a stepping stone to show that new therapies from natural, complex mixtures can be developed to meet the quality and clinical trial requirements of the FDA (C. Wu et al., 2020). Mytesi (previously known as Fulyzaq) was the second botanical NDA to be approved, in 2012. Mytesi is an extract called *crofelemer,* harvested from the red bark sap of the *Croton lecheri* tree, and used for the treatment of drug-induced diarrhoea that is caused byAIDS/HIV medication. The third botanical NDA approval occurred in 2018 for the cannabidiol (CBD) based product Epidiolex. Epidiolex is based on CBD extracted from the cannabis plant, and is used to treat seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in children. The approval of Epidiolex was not only another win for botanical drugs in meeting the standards set by the FDA, but also marked a major success for cannabis-derived drug products in the US (Lokhande & Lokhande, 2018; C. Wu et al., 2020).

Chapter 3: Literature Review

To further elaborate on the research objectives, the literature review will be split into two parts. Part 1 focuses on firm management, firm strategy and risk mitigation literature. Part 2 focuses on the regulatory literature, regulation in the pharmaceutical and biotechnology industry and regulatory challenges specific to botanical drug development. Furthermore, this literature review illuminates the gap in the literature which this study thereafter aims to address.

3.1 Part 1: Firm management

There is little literature specifically focused on management strategy in the botanical drug development space. As previously mentioned, botanical drug development is held to the same regulatory standards as conventional drug development and therefore relevant literature from the biotechnology field has been utilised for this section of the literature review due to the similarities between the two.

Biotechnology can be defined as the application of the principles of engineering and biological science to create new products from raw materials of biological origins such as vaccines, drugs, and foods (Verma et al., 2011). Typically, biotechnology firms run leaner and are more innovative than larger pharmaceutical companies who have access to significant resources (Noonan, 2021). Biotechnology firms have become the innovators and risk takers of the industry, who often aim for exit strategies via acquisition by incumbent pharmaceutical firms (Noonan, 2021). In contrast, large pharmaceutical firms who are rigid with multiple layers of management, are growing increasingly risk averse and focusing on late-stage drug development to fuel their growth via acquisitions and licensing deals, rather than conducting research and development themselves (Burns et al., 2009; Noonan, 2021).

Innovation and product development in the biotechnology industry is a complex and risky activity which demands appropriate skills and knowledge due to the high levels of ambiguity and large resource strains (Drakeman & Oraiopoulos, 2020a; Radas & Bozic, 2012). This high risk and ambiguity is largely due to our limited understanding of complex biological systems which makes drug research and development challenging (Pisano, 2006). Decision-making is the core function of any firm undergoing the drug development process, as it requires managers to be highly innovative, while simultaneously being constrained by strict regulations and financial capabilities (Jekunen, 2014). Drug development is tightly connected with timing as financial obligations typically follow closely behind the developmental phases

of a drug, each of which have specific resource requirements and require managers to make key decisions regularly (Jekunen, 2014).

Managers must use available information to facilitate decision-making that both increases the firm's probability of success and minimises damage where failure is unavoidable. Firms must be able to cull the development of their products which are destined to fail developmental milestones as early as possible to minimise loss of capital and further damage to the firm (Jekunen, 2014). It is common; however, for firms to delay culling a failing project based on the managers inability to cut losses, and therefore it is also important that managers know when a project is performing poorly though planning and measuring of developmental performance (Godener & Söderquist, 2004; Jekunen, 2014).

There is a positive relationship between the extent of planning, and the performance of a firm (Jekunen, 2014; Kaplan & Norton, 2007; Lyles et al., 1993; Shimasaki, 2009a; Wong, 2011). Typically, the success factors in high-technology industries are classified into three broad categories: strategy, management characteristics and the competitive environment (Brown & Eisenhardt, 1995; Woiceshyn & Hartel, 1996). While the strategy and management characteristics are especially important in the success of novel biotechnology firms such as those developing botanical drug products, the competitive environment has been recognised to have limited effect on a firm's prospects of success, especially in the newly developing botanical drug industry (Drakeman & Oraiopoulos, 2020b). The competitive environment has little influence on success as the space in which most innovative firms operate is generally uninhabited and not influenced by patent protection (Drakeman & Oraiopoulos, 2020b).

Top performing firms in the biotechnology and pharmaceutical space have well established drug development strategies and often engage in collaborative alliances with universities, manufacturers, suppliers, other firms, and various industry professionals (Shimasaki, 2009b; Woiceshyn & Hartel, 1996). Despite established product development strategies and collaborative alliances, poorly performed project and risk management can cause missteps in the regulatory process potentially costing millions of dollars, derailing alliances, causing years of delay in drug development and even closure of the firm (Shimasaki, 2009b).

Thorough planning of development strategies can help to mitigate challenges which may arise from unfavourable developmental setbacks and resource shortages, both of which are typical bottlenecks in the development of a new drug product (Jekunen, 2014; Radas & Bozic, 2012; Shimasaki, 2009b). While

all innovative drug products (botanical or not) face unique challenges, good management of drug development activities entails efficient allocation of resources, undertaking risk analysis, and measuring developmental performance and progress to inform future decision making. These are discussed further in the sections below.

3.1.1 Strategy

Firms select strategies they hope will create and sustain a competitive advantage in their field, and which will lead to meaningful results and superior financial returns (Kaplan, 2009). A key trend in research and development is the increasing orientation towards firm internalisation which requires adoption of a more commercial focus to produce outcomes of longer-term potential (Francis, 1992; Lux et al., 2021). As highlighted by (Lux et al., 2021), for a firm to understand all its options and target indications during early drug development, its primary early priority should be achieving a consensus on corporate strategic imperatives. For example, is the firm aiming for an exit strategy after clinical proof of concept, via licensing or an acquisition, or is the firm aiming to develop, market and launch the drug product itself? This idea has previously been highlighted by Gans & Stern's (2003) central proposition that value gained through innovation may be earnt through the product market or through the market for ideas, and that making the decision between the two is a key element in drug commercialisation strategy. This is further depicted by Gans & Stern's (2003) model of commercialisation framework strategy (refer to Table 1) which builds on the work of Teece (1986), linking strategy and the commercialisation environment by showing the circumstances in which an innovative firm may develop their own value chain (developing, manufacturing, and marketing themselves) or integrate into an existing value chain (via licensing or acquisition). By achieving consensus and developing an overarching strategy, firm progression is enhanced through better activity harmonisation, a reduction in conflicting or competing work and greater symmetry with the wider business (Huang et al., 2002; Rao, 2022).

		Do incumbent's complementary assets contribute to the value proposition from the new technology?	
		No	**Yes**
Can innovation by the start-up preclude effective development by the incumbent?	**No**	**The Attacker's Advantage**	**Reputation-Based Ideas Trading**
	Yes	**Greenfield Competition**	**Ideas Factories**

Table 1: Table of Gans & Stern's model of commercialisation strategy (Gans & Stern, 2003).

In the biotechnology sector, the availability of intellectual property protection alongside the regulatory, developmental and distribution capabilities of incumbent pharmaceutical companies makes negotiating in the market for knowledge (licensing or acquisition) a lucrative commercialisation strategy (Gans & Stern, 2003; Lux et al., 2021; Seldon, 2011).

Gans & Stern (2003) provide a useful first point of reference for a firm developing a commercial strategy, alluding to competitive or cooperative strategies with incumbents, but failing to examine the complexity of what practitioners do during the commercialisation processes, and as such Gans and Stern do not apply a useful framework–particularly for the development of a complex product such as a botanical drug. Gans & Stern's (2003) commercialisation strategy does not consider the ability for firms to simultaneously cooperate with both internal and external capabilities to streamline strategic decision making (Rao, 2022).

Pisano (2006) recognises that biotechnology firms developing novel products can strategize to develop their product for the market or the market for ideas. Pisano (2006) adds further dimensions to Gans and Stern's model of commercialisation strategy, with the idea that for biotechnology firms to optimally perform they must integrate across different disciplines and parties as the process of drug development

cannot be broken into independent pieces. Pisano (2006) proposes this can occur externally if firms aim to form greater horizontal integration through licensing and strategic collaborations within the industry. He proposes that the utilisation of complementary assets such as knowledge sharing between alliances will increase the knowledge base of the firm during drug development and thus increase the likelihood of success through more informed decisions (Pisano, 2006).

Pisano suggests that different business models may be viable for different technological innovations depending on which of the four broadly classed technological innovations the product falls within (Pisano, 2006, p. 166). Those four classes of technological innovations are: novel research methods and tools; novel mechanisms of actions or targets; novel compound types and novel treatment modalities (Pisano, 2006, p. 166). Botanical drug products fall within Pisano's definition of a "novel compound type" which typically contain two features; information asymmetries and notable levels of tacitness (Pisano, 2006, p. 170). First, information asymmetry is the difference in information available between the potential collaborators (or buyers) and the innovators (sellers), which act as barriers to accessing the market for knowledge (Pisano, 2006). Second, tacitness refers to the knowledge which is not fully articulated or able to be described by those who possess it (Pisano, 2006). Pisano (2006) recommends that products that fall within the novel compounds category should strategize to achieve vertical integration with their downstream assets (developmental, manufacturing and distribution). This recommendation falls in line with botanical drug development based on the regulatory requirements for specialised cultivation processes and manufacturing facilities, which differ from synthetical chemical manufacturing and are specific to each botanical drug product (Wu et al., 2020). Vertical integration may reduce the risks of operating in an inefficient market for know-how but brings with it other risks such as larger regulatory and funding requirements (Pisano, 2006). Furthermore, firms which are following this strategy may be at higher risk due to everything resting on the success of a single therapeutic product (Pisano, 2006. Pisano (2006) also highlights that following a vertical integration strategy, collaboration (integration with the existing supply chains) may be a second-best strategy based on historic accounts of high legal disputes of products within the "novel compound type" category.

Pisano (2006) contributes to biotechnology strategy literature by examining the relationship between a technology type and the business strategy a firm should follow. Like Gans and Stern (2003), Pisano's recommendations are provided at the industry level and supply useful frameworks in which firms may consider in their firm strategies. However, Pisano's contribution is limited for two reasons. First, he does

not explicitly recognise any of the strategic choices which must be made prior to choice of business model strategy. Second, he does not provide guidance for individual firms seeking to increase their chances of success due to his focus on the industry level.

There is little literature on the specific challenges of firm level strategic planning for biotechnology firms, as most strategy approaches proposed are no different to those proposed for other industries (Figure 2) (Ahn, 2017; Molloy & Johnson, 2016). The process of strategic planning traditionally follows a linear progression through distinct stages such as firm vision, situation analysis, goal formulation, strategy development, strategy selection and strategy implementation (Molloy & Johnson, 2016).

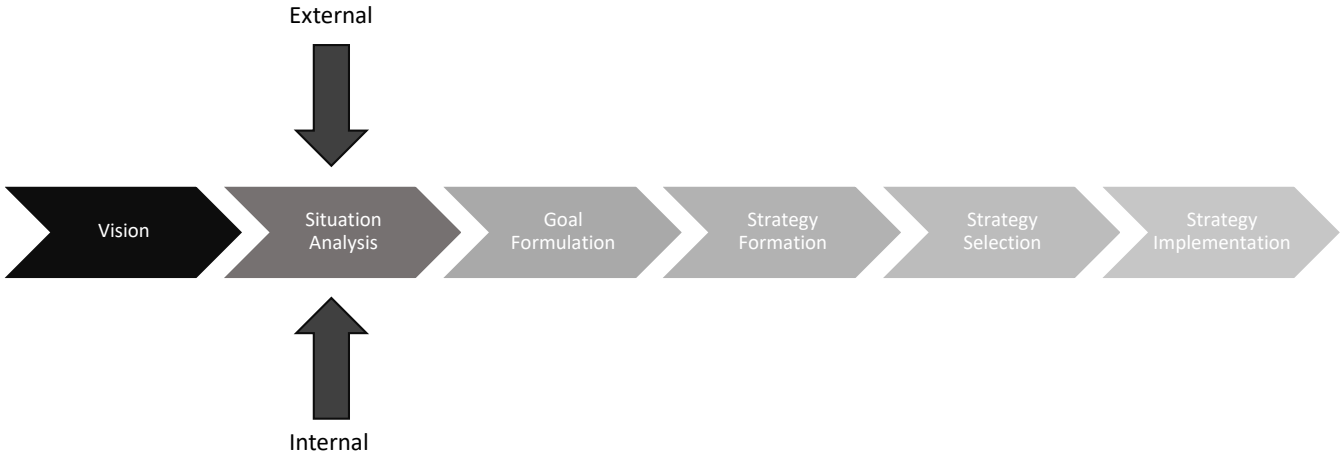

Figure 2: The strategic planning process adapted from Muller (2002).

The vision represents the initial goal of the firm, the therapeutic target area or population. Although many firms may be good at managing specifics in drug development, they may not have an all-inclusive development strategy which supports the overall firm vision (Huang et al., 2002; Jekunen, 2014). Muller (2002) stresses the importance of a clear firm vision, as it enables biotechnology firms to maintain sight of the superordinate goals during the high levels of uncertainty and complexity during the lengthy drug development timeline.

The analysis stage consists of examination of the external and internal firm environments and typically involves SWOT analysis (strength, weakness, opportunities, and threats) (Molloy & Johnson, 2016; Muller, 2002). External firm environments consist of political, social, technological, regulatory and industry developments and trends, while internal environments generally consists of management know-how, firm knowledge and skill strengths and weaknesses (Molloy & Johnson, 2016).

Goal formation, strategy formation and strategy selection uses the information gathered during situation analysis to choose from different generic strategies (Malone et al., 2008). Furthermore, it is at this point where firms decide on their business model and how they plan to integrate within their industry (such as vertical or horizontal integration) (Muller, 2002). During the implementation stage, strategies are translated into actions by the firm. These actions are likely to change because of the uncertainties and complexities of the drug development business, in conjunction with the turbulence of both regulatory and funding requirements (Molloy & Johnson, 2016).

The strategic planning theory does not work in all situations because the stages presented may be oversimplified and detached from one another (Mintzberg, 1978). Molloy & Johnson (2016) argue that attempting to prescribe boundaries to a biotechnology firm in the form of the strategic planning process is likely to prove counter-productive in practice. This is due to the unique regulatory, funding and temporal challenges faced by the industry which often require dynamic strategy adjustments which should not be constricted early-stage planning (Molloy & Johnson, 2016).

Mintzberg (1978) describes the stage-related strategic planning procedure as the intended strategy and defines strategy in general as a succession of directed decisions. When the intended strategy (or sections of) comes to fruition, this is termed as the realised strategy (Mintzberg, 1978). Mintzberg (1978) defines strategy as a stream of unrestricted, strung together decisions and can be viewed in both a prospective and retrospective manner. Where the prospective requires that strategies are planned with intention, the retrospective allows for strategies to be formed gradually as the intention may not necessarily be realised due to the changing complexities of the biotechnology space.

Mintzberg (1978) illustrates how the intended and realised strategy forms a continuum, where somewhere between the deliberate and emergent strategy is where the real-world strategy exists (refer to Figure 3). This real-world strategy can be formed from the combination of the intended and realised in three different ways:

1. Intended strategies that are realised are termed deliberate strategies.
2. Intended strategies that are not realised are termed unrealised strategies.
3. Realised strategies that were never intended are termed emergent strategies.

Strategies may not be realised due to unrealistic expectations, misjudgements about the current environment or due to changes in the strategy during development (Mintzberg, 1978). Emergent strategies form due to displacement of the intended or due to circumstances emerging that were never strategized to begin with (Mintzberg, 1978).

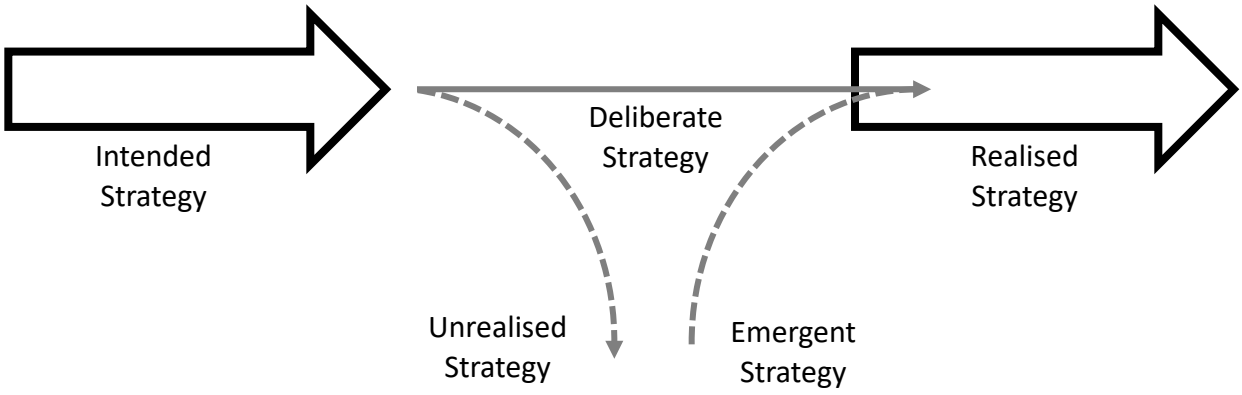

Figure 3: Real-world strategy, adapted from Mintzberg (1978)

Understanding how to develop effective strategies in the biotechnology sector requires detailed understanding of key characteristics and relationships in the industry, and how these will drive essential elements of a firm's success. Contributions to strategic management research in the biotechnology sector have been largely concentrated on the industry level structures and relationships such as the work portrayed by Gans & Stern (2003) and Pisano (2006). Whereas strategy process and context research such as that presented by Mintzberg (1978) and Muller (2002) describe how strategies are formed and what an effective strategy may be but fail to explain how toachieve an effective strategy.

3.1.2 Risk and uncertainty

Strategy is about moving the company forward and performing optimally. Measuring and managing strategy differs substantially from measuring and managing risk (Kaplan, 2009). Risk managementis about identifying, avoiding, and overcoming obstacles that strategy may encounter along the way (Kaplan, 2009). Avoiding risk does not advance the strategy, but risk management reduce hurdles and barriers that would otherwise prevent the firm from reaching the desired strategic target (Kaplan, 2009).

To improve the chances of success, firm managers must understand risk and uncertainty to address all likely hurdles as early as possible in an anticipatory, not reactive, manner (Kaplan, 2009; Shimasaki, 2009a). Risk and uncertainty is inherently present in any business venture, however innovative science-based industries, such as the biotechnology sector, carry the highest risk and uncertainty of all (Cleary et al., 2021; Wong, 2011). Wong (2011) makes a clear distinction between scenarios with risk and scenarios with uncertainty. Risk may be mitigated with calculated informed decisions based on prior knowledge about potential outcomes, while uncertainty is difficult to navigate due to little to no previous experience.

Biotechnology start-ups are perceived to be inherently risky and highly uncertain as they typically form around a single lead drug candidate, long timelines of product development, are often ascribed to a 90% failure rate, and they generally generate no substantial revenues until approval and sale of products (Cleary et al., 2021). This is not different in the botanical drug industry. Examples of these risk and uncertainties can be found in Table 2.

Recommendations from within the literature suggest one way to minimise risk is to have backup drug candidates within a firm's development pipeline or further lead compound indications in case it is necessary to cease development of the lead compound (Graves et al., 2000; Hernández-Cuevas, 2007; Jekunen, 2014; Patel et al., 2013). Although, this is not necessarily an option available to the majority of biotechnology firms who are in their infancy and lack both financial and experienced managerial resources.

Risk	Uncertainty
• Financial risk – liquidity risk, funding availability, investor attractiveness, cost of capital, long returns on investments • Operational risk – management experience, staff skill, legal and intellectual property risks, supply-chain risks, manufacturing risks • Environmental risk – regulatory requirements, market changes, social, economic, political and physical risks • Technical risk – tacitness of technology, compound molecule risks, mechanism risks, product stability • Safety & efficacy risk – product abuse and misuse risks, side effects risks, meaningful clinical trial data	• Financial uncertainty – interest rate changes, lending criteria changes, financial crisis • Market uncertainty – buyer demand, consumer behaviour, competitor development in the space, firm reputation • Technical uncertainty – clinically meaningful study outcomes, drug mechanism working in humans, side effects, scaling and manufacturing issues, regulatory requirements appeased, satisfactory manufacturing and cultivation sites, • Temporal uncertainty – product development timeline, further studies/ information requests by regulators, market launch uncertainties

Table 2: Table of examples of risk and uncertainty in the biotechnology and botanical drug development space (Ahn, 2017; Bode-Greuel & Nickisch, 2008; Pisano, 2006; Shimasaki, 2009a; Vanderbyl & Kobelak, 2008; Wong, 2011).

Risk mitigation is about increasing the probability of success through gathering information and breaking down barriers impeding firm strategy (Wong, 2011). Through such information, firm managers can measure firm performance, estimate risk factors, and plan and forecast key firm and developmental activities (Kaplan, 2009; Shimasaki, 2009a; Wong, 2011). The continual analysis and management of risk is vital for the maximisation of firm success and therefore risk analysis and risk management should be an integral part of firm strategy (Shimasaki, 2009a).

Risk can affect any aspect of a firm, as there are multiple dimensions of risk. The risk management literature discusses the nature and types of risk involved in various industries (Drakeman & Oraiopoulos, 2020b; R. S. Kaplan, 2009; Molloy & Johnson, 2016), Although few authors discuss the specific risks involved in the development of biotechnology firms such as Shimaski (2009). With over three decades of experience within the biotechnology industry and through many observed failures, Shimasaki (2009) has

generated a Biotech Evaluation Tool highlighting the different types of risk that will need to be successfully managed by biotechnology firms to survive (refer to Table 3).

1. Management	2. Technology	3. Market	4. Regulatory	5. Financial
• Experienced CEO that has demonstrated they can lead the organisation successfully • Experience of managers and wider team with relevant industry experience • Awareness of skill gaps/ weaknesses in management team • Expertise of staff to execute the current business plan	• Firm contains top technical or scientific staff that have demonstrated leadership in the field • Established prototype, proof of concept or other supporting information • Novelty of innovation and degree of applicability and relativity to industry • Level of IP protection indicating freedom to operate within the field • Future of innovation, is it a core technology or just one product and are there potential future products from this technology	• Product market demand or possibility of demand has been indicated • Market strategy formed with indication of market need and evidence of performance of possible substitutes • Market size and market share returns are adequate to sustain firm • Competitor and market convergence analysis to determine positioning and demand for innovation • Market entry and distribution channel strategy formation • Company has the required knowledge and capabilities to facilitate market entry and distribution channel formation	• Knowledge of the regulatory requirements surrounding the innovation and awareness of any possible regulation changes that may occur • Strategies formed by team members for process and temporal specifics of regulatory approval • Risk profiles on product development and firm resources • Examples of other successful innovations which can influence firm strategy • Expertise of managers and staff in regulatory affairs • Relationships and communication with regulators and external regulatory experts	• Funding potential based on similar innovations • Eligibility for investment has been determined based on VC funding trends • Exit strategy has been formed • Strategic financial forecasts with requirements for different milestones including market approval has been developed • Cash reserves for emergency business costs

Table 3: Table of Biotech Evaluation Tool adapted from Shimasaki (2009, p. 50)

In addition to the broad range of risk a firm may face, not all risks pose the same threat to a firm's survival or integrity. Kaplan (2009) classifies risk into three broad hierarchical levels as represented in Table 4. Level 1 represents the risks that are known to firms, level 2 represents the risks that firms know they do not know, and level 3 represents the risks that firms do not know that they do not know (Kaplan, 2009). Risk associated with uncertainty can be attributed to both level 2 and level 3 risks, as uncertainties exist in the realm of the unknowns (Kaplan & Murray, 2010). Typical uncertainties that biotechnology firms may face exist surrounding the safety of the innovation, whether the lead compound may show clinical significance and the degree to which buyers may be willing to spend on the innovation (Gans & Stern, 2003; Kaplan & Murray, 2010). Firms who have a comprehensive risk

management programme integrated with their firm strategy have a competitive edge when it comes to attracting capital, as investors feel as if their investment is protected from unexpected disastrous scenarios (Vanderbyl & Kobelak, 2008).

Level 3: Routine Operational and Compliance Risks	Level 2: Strategy Risks	Level 1: Global Enterprise Risks
• Risks associated with every day processes • These risks may expose the firm to fraud, negligence, legal and regulatory liabilities and expensive regulatory litigations if not adequately managed • Examples may be errors in maintaining and updating financial and tax systems, protecting information and assets and ensuring information security and backup data is in place. • These risks are known and are avoidable	• The major plausible risks inherent to the strategy • These risks may expose a firm to large regulatory and financial constraints which may cause significant damage to the firm if not adequately managed • Examples may be customer, brand, supply chain and reputation risks, innovation, environmental, human resource, regulatory, clinical trial, safety and information technology risks. Although these risks are highly dependent on the strategy • These risks often have sufficient associated historic data enabling risk mitigation practices to be put in place	• Unpredictable, unprecedented occurrences that create existential risk to a firm • These risk generally expose a firm to existential risks and are completely unknown • Examples may range from drastic changes in oil and interest rates through to natural disasters such as the destruction of a botanical drug firm's cultivation facility • These risks are unknown to firms have no historic data to leverage
"Known risks"	*"Known unknown risks"*	*"Unknown unknown risks"*

Table 4: Table of hierarchical risk levels adapted from Kaplan (2009).

Kaplan emphasises that for firms to be successful, risk management must be taken seriously and a large proportion of managers and senior executives fail to spend sufficient time planning and discussing risk (Kaplan, 2009; R. Kaplan & Norton, 2007). Furthermore, Kaplan found that many managers and senior executives did not consider management of risk and uncertainty as a priority and would delegate these tasks to risk professionals who were often siloed from other decision makers (Kaplan, 2009). Risk management requires predicting events, particularly unlikely ones that have never occurred before. But despite the difficulty of risk management, managers who avoid, play down the importance, or delegate the task do so at their peril (Kaplan & Norton, 2007).

Studies from several different industries have shown that actively undertaking risk management has positive correlations with financial performance, shareholder value, investor attention and allocation of resources within the firm (Raz & Michael, 2001; Vanderbyl & Kobelak, 2008). It is possible for firms to navigate and prepare for even level 1 risks and uncertainties through processes such as forecasting, brainstorming and exploring uncertainties (Ekanayake & Subramaniam, 2012; Wong, 2011). To break

down any possible barrier and reduce the chance of failure, Vanderbyl & Kobelak (2008) recommend that biotechnology firms should integrate sophisticated risk management tools into their strategic planning process.

There are a range of managerial strategies which can be effectively implemented to help mitigate risk and uncertainty during firm and drug development. Two of which may have particular use in the biotechnology and drug development area are “real options reasoning” and “stage gate planning” (Cooper, 2008; Miller & Waller, 2003).

3.1.2.1 Real Option Reasoning

Real options reasoning is a viable strategy tool for risk and uncertainty management in biotechnology firms as the investment in options occurs sequentially as does the development of a drug product (McGrath & Nerkar, 2004; Miller & Waller, 2003). Faced with uncertainty, real options give management the flexibility to acquire, divest or switch resources when such move may be considered necessary (Miller & Waller, 2003). Real options reasoning is also used as an investment tool to assess projects based on their net present value (NPV) and their potential future value after undertaking certain options.

The sequential process of real options consists of three distinct stages, as shown in Figure 4. The first stage starts with the recognition of an opportunity of an option, such as the investment into a potential new botanical drug. The second stage consists of analysis to determine whether further investment into the option is justified. This occurs through reduction in uncertainties over time, the creation of new knowledge central to the option or by increasing the value of the option (McGrath & Nerkar, 2004). Examples include; the greater acceptance or understanding of botanical drug pharmacology over time, further research surrounding the specific pharmacological interactions of the product, and positive results obtained from the product in clinical trials, respectively (Bode-Greuel & Nickisch, 2008). The third stage of real option reasoning relies on the new value of the option, where firm managers will decide whether to invest in the option and further progress it towards a predetermined end goal, to liquidate the option in the market for knowledge to minimise losses, or termination of the option (Gans & Stern, 2003; McGrath & Nerkar, 2004; Miller & Waller, 2003).

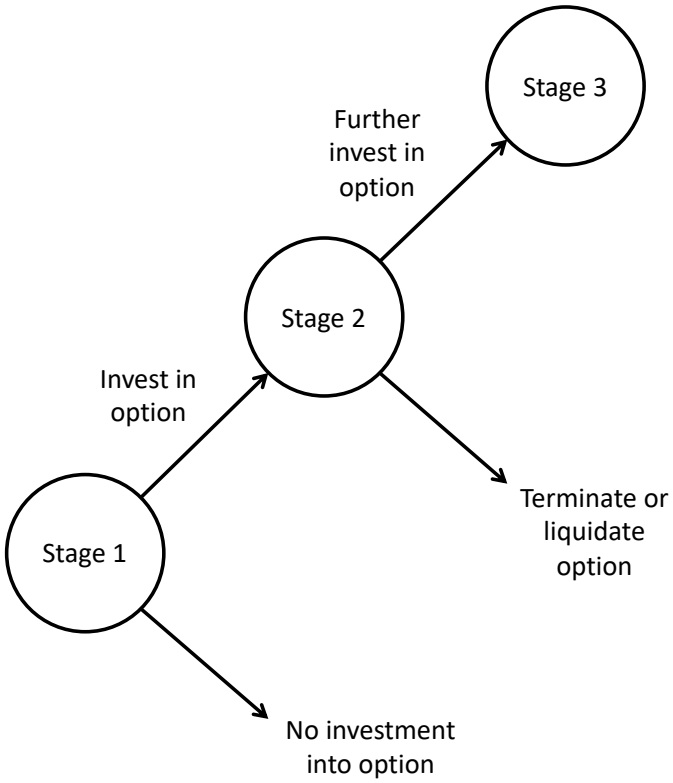

Figure 4: Real options reasoning, adapted from (Adner & Levinthal, 2004)

Biotechnology and pharmaceutical product development involves sequential strategic decision making and long developmental timelines with costs that increase with product maturity, making real option reasoning applicable in this space (McGrath & Nerkar, 2004; Noonan, 2021). Real option reasoning is a flexible risk management strategy that supports investment into options over time, aids managers' risk management and strategic decision making and helps map out the possible resource value pathways facilitating estimates of an option's value at a specific time (Adner & Levinthal, 2004; Miller & Waller, 2003). Furthermore, the real option approach to strategic risk and uncertainty management parallels the "emergent strategy" coined by (Mintzberg, 1978), as it facilitates differentiation of strategy from the intended strategy over time as new information and development choices for options occur.

3.1.2.2 Stage-gate decision process

The stage-gate decision process is a robust idea-to-launch decision process which divides the undertaking of new product development into distinct stages separated by managerial decision gates (Cooper, 2008). As depicted by Figure 5, the stage-gate decision process consists of a series of individual stages (Cooper, 2008). At each of these stages the firm will gather information to reduce developmental risks and uncertainties (Cooper, 2008). Following each stage is a gate, where management will make a kill/go decision based on deliverables (the accumulated data of the stage) and the criteria (milestone criterion against which the product is judged) (Bode-Greuel & Nickisch, 2008; Cooper, 2008).

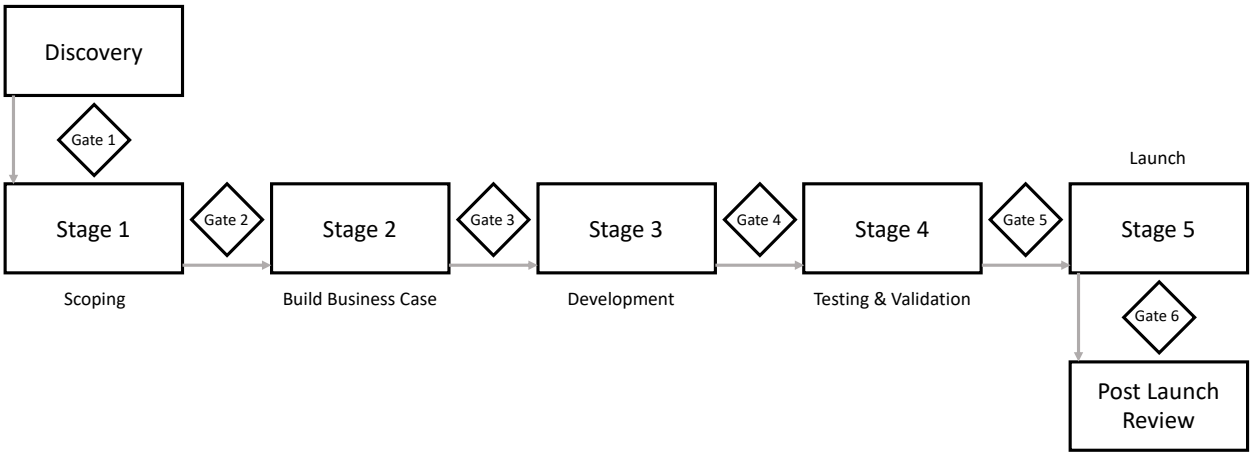

Figure 5: Stage-gate decision process for new product development, adapted from Cooper (2008)

The stage-gate decision process is a well established principle in the pharmaceutical industry as the decision processes are related to the major clinical and preclinical development milestones (Bode-Greuel & Nickisch, 2008; Dolgos et al., 2016). The stage-gate decision process is adapted to the individual requirements of the product which is being developed (Cooper, 2008). Each stage may consist of multiple tasks which may run in parallel or sequentially to one another before arriving at the gate (Bode-Greuel & Nickisch, 2008). Stages and gates are also dynamic in structure and may change based on the emergence of new data (Cooper, 2008). Emergent strategies may occur during stages resulting in more than one way forwards at a gate. Examples include the identification of a drug's side effect being beneficial, and thus the possibility to investigate another treatment schedule emerges (Bode-Greuel & Nickisch, 2008). Gates also facilitate resource allocation. With the decision to move a drug product into the next phase, resources, either internal or external, must be allocated (Bode-Greuel & Nickisch, 2008).

Resource allocation is particularly beneficial for firms who are developing a portfolio of drug products as it ensures that the required resources are not already being utilised by other products in development (Bode-Greuel & Nickisch, 2008; Dolgos et al., 2016). A summarised representation of the stage-gate decision process is depicted in Figure 6.

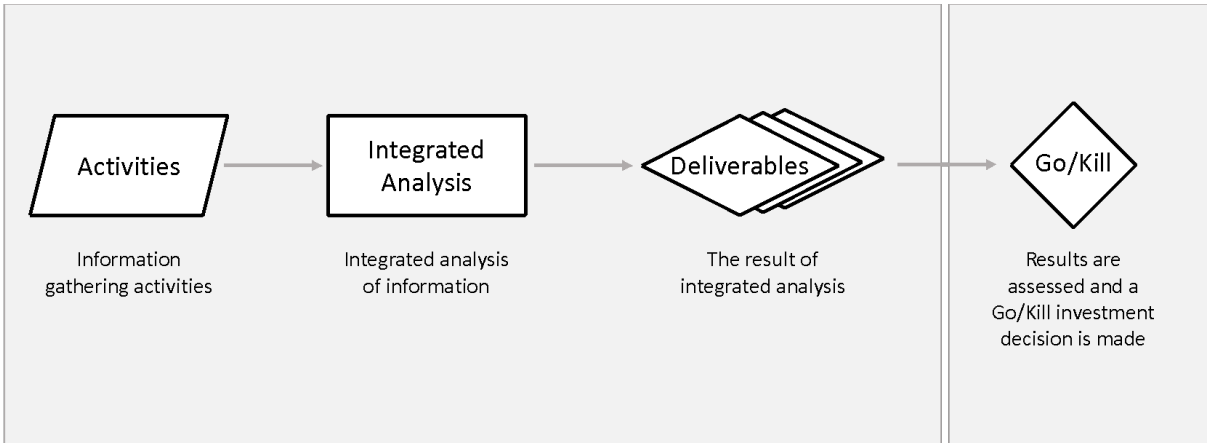

Figure 6: Summarised representation of the processes at each step of the stage-gate decision process, adapted from Cooper (2008).

3.2 Part 2: Regulatory Environment

The purpose of this section is to discuss two relative regulator approaches identified from the regulatory literature, define key concepts identified within the regulation of the pharmaceutical and biotechnology industry, and elaborate on the major regulatory challenges associated with developing botanical drugs.

3.2.1 Regulation

Regulation is defined as a process for assessing and analysing the delivery of defined activities (Marsden et al., 2020). These activities are compared against a framework of ideas and standards which are based on widely accepted evidence and good practice in relation to quality (Marsden et al., 2020). Regulation approaches and firm behaviours can help design concepts which may help firms in strategizing and risk management when developing innovations for market. There are several different regulatory approach theories within the literature that describe the complex relationship between regulators and firms, though few fit the context of drug development. There is a lack of regulatory theory that assesses the relationship between regulators and firms in botanical drug development. Two generic regulatory approaches from the literature have been identified, the 'responsive regulation approach' and the

'system based regulation approach', and are included in this section due to their applicability to drug development (de Bree & Stoopendaal, 2020; Marsden et al., 2020).

3.2.1.1 Responsive regulation approach

Responsive regulation approach, developed by Ayres & Braithwaite (1992), is based around the idea that the type and scale of a regulatory response to a firm's innovation is dependent on the motivations, actions, and behaviour of the regulated firm. Responsive regulation approach suggests that firms are supported by the regulators through rewarding compliance, while issuing sanctions for non-compliance, thus persuading firms towards meeting standards or making improvements, while creating a balance between persuasion and punishment (Nielsen & Parker, 2009). This balance is supported by the regulator's ability to engage with firms along an enforcement scale, from recognition and reward through to both minor and severe sanctioning where necessary (as highlighted in Figure 7) (Ayres & Braithwaite, 1992; Braithwaite, 2006).

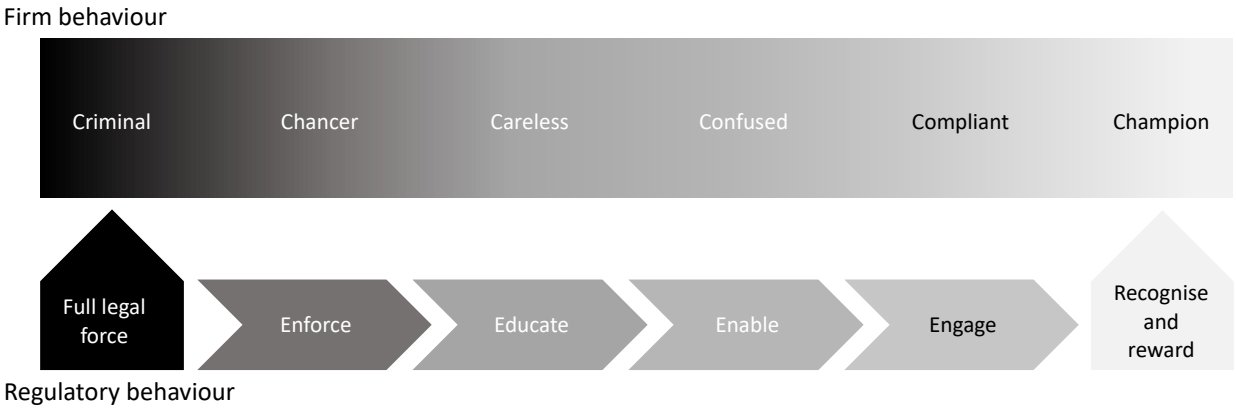

Figure 7: Figurative representation of the responsive regulation theory adopted from (Braithwaite, 2006).

Central to responsive regulation approach is that those being regulated must believe in the unavoidable nature of the sanctions, as requests followed by punishment only work when firms know that sanctions will follow non-compliance with regulations (Healy, 2016). Therefore, the looming threat of sanctions acts as a guarantor that firms will comply with the more conciliatory approaches of the regulator (Healy, 2016). Responsive regulation approach also suggests the existence of a tripartism, where the regulatory process includes the regulator, the regulated, and other stakeholders who further entice compliance by firms (Ayres & Braithwaite, 1992). These stakeholders may be investors and potential business partners

who show further interest in an innovative drug product once regulatory milestones have been obtained. These stakeholders are important as they can help ensure and support improvement of firm compliance (Ayres & Braithwaite, 1992).

Marsden et al, (2020) highlights that for responsive regulation approach to work effectively, several important factors are required and must be upheld by the regulatory staff. These factors include: a high level of appropriate staff training; expert communication and relational skills; the ability to rebuild trust after enforcement and consistency across all the aforementioned (Beaussier et al., 2016; Marsden et al., 2020). Furthermore, there should be continuous communication between regulator and firm to ensure the adequate conveyance of complex messages and to understand the challenges and struggles of the firm (Nielsen & Parker, 2009).

3.2.1.2 System based regulation approach

System based regulation approach is a concept where regulated firms use their existing management, which may have originally been formed to ensure quality and compliance, to ensure self-regulation of the firm (de Bree & Stoopendaal, 2020). In this approach, the regulator monitors a firm's capacity to self-evaluate through its internal management and processes. Rather than the regulator having a prescriptive or reactive approach to regulation of firms, the regulator promotes 'meta-regulation' to occur within firms so that proactive, self-assured quality standards can be developed by the firm to match the expectations set by the regulator for the industry (de Bree & Stoopendaal, 2020; Marsden et al., 2020).

This concept is built around the idea that regulators want to promote firms to self-govern, so that there is a greater synergy between the processes and goals of the firm and the expected processes and goals of the regulator (Marsden et al., 2020). Regulators may attempt to initiate this synergy through several different activities. Synergy promoting activities include auditing, observations, discussions and interrogations of management and governance systems and processes (de Bree & Stoopendaal, 2020). The goal is to form an ongoing relationship to help the firm identify gaps in their processes and challenge the way these systems work in practice (Marsden et al., 2020).

3.2.2 Regulation in the pharmaceutical and biotechnology industry

Regulation is a necessary part of life sciences, especially within the pharmaceutical and biotechnology industry due to the various health risks that patients may face when consuming drug products. Unfortunately, Western drug regulation has formed largely in response to drug induced disasters, rather than the evolution of knowledge base (Rägo & Santoso, 2008). Two such disasters are particularly worth mentioning. First, was the diethylene glycol poisoning of 1937 following the use of an ill-prepared antibiotic sulphanilamide elixir, which killed over 100 people (Abraham, 2003). Second, was the morning sickness medication, thalidomide, which caused thousands of birth defects between 1957-1961 (Abraham, 2003; Rägo & Santoso, 2008). These two tragedies marked the establishment of the Federal Food, Drug and Cosmetic Act (FDCA) of 1938, the first regulation which required that all drugs be labelled with adequate directions for safe use, and the Kefauver-Harris Amendments of 1962 requiring all new drugs to be proven safe and effective (Abraham, 2003; Kille, 2017).

Regulators must ensure products are developed with high level quality without restricting innovation (Thakkar et al., 2020). As conceded by Olson (2014), regulators such as the FDA strive to protect and advance public health by pursuing two main goals: ensuring drug safety, quality and effectiveness; and facilitating public access to clinically useful drugs (Olson, 2014). Unfortunately, the pursual of one of these goals, often leads to a reduction in the chance of achieving the second goal, as the stringent clinical milestones and regulations designed to withhold ineffectual and harmful drugs from entering the market may delay patient access to new medicines (Olson, 2014). Alternatively, an increased access to newly developed drugs by decreased regulatory stringency and review time could lead to the approval of products with low efficacy and/or cause severe health implications (Abraham, 2003; Olson, 2014). This trade-off between timely market access and drug efficacy and safety is a central challenge faced by regulators, as they attempt to find the right balance between the possible cost of ineffective or dangerous drugs potentially entering the market, and the cost of delaying approval of beneficial drugs which are in demand (Olson, 2014).

While patients demand protection from unsafe or misbranded products, businesses and sometimes patients alike complain that regulations are an impediment to drug development (Kille, 2017). The 1962 Kefauver-Harris Amendments (KHAs) have been claimed to add up to a decade of regulatory delay to drug development, which has also greatly increased the cost of such development (Kille, 2017). For example, following the 1962 KHAs, it was estimated that the new drugs getting to market fell by around

60% while the cost of pharmaceutical research and development witnessed a 20-fold increase (Hooper, 2008). Regulations are designed with the patient's health and safety as the top priority, and firms must stay compliant with these regulations to uphold their financial and corporate integrity, and to legally sell their products on market (Altamuro et al., 2022; Hooper, 2008).

Evidence about the drug's benefits, risks and overall performance is critical for safe and effective use. Without accurate information about drug quality, physicians and patients may make inappropriate drug choices and suffer negative health consequences (Olson, 2014). A range of regulatory activities over the course of a drug's life cycle ensure efficacy, safety and quality of the drugs available to patients (Olson, 2014). These activities include premarket evaluation of new drug candidates, inspection of manufacturing facilitates, regulation of drug labelling and marketing activities, and post-market surveillance of drugs to ensure ongoing efficacy (Olson, 2014). Most regulatory authorities follow similar procedures of requiring data to confirm product safety and efficacy, although, the level and source of data required for approval varies between countries (Checo et al., 2019; Thakkar et al., 2020).

The partnership between firms and regulators may at times be contentious, but is ultimately beneficial to all (Haigney, 2016). Although the pharmaceutical and biotechnology industry support the regulation of products to ensure intellectual property protection and buyer trust in safety and efficacy, regulatory issues still present a considerable challenge to many firms (Ahn, 2017; Haigney, 2016). These challenges are compounded in novel therapeutic areas where regulations are constantly evolving and basic regulatory practices are based upon ill-fitting principles and guidelines for already existing product categories (Nieminen et al., 2004). Ahn (2017) argues that many international sponsors who fail within the US botanical drug route do so due to a lack of an internationally harmonised regulatory system, as sponsors are often not aware of the practical differences required between regulators. Furthermore, the case-by-case evaluation of polymolecular botanical drugs based on the historic single molecule regulatory pathway, with only three successful NDAs to date, has not yet provided the industry with a clear framework for how to successfully develop botanical drugs for the US market (Ahn, 2017; Checo et al., 2019; Dou et al., 2019b; Liu & Wang, 2008; Nieminen et al., 2004; Wu et al., 2020).

3.2.3 Botanical drug regulation and challenges

The reality of the biotechnology and pharmaceutical industry is that firms can raise sufficient capital, possess strong patent portfolios, successfully complete lengthy development processes, and identify key product markets for their new product, but without meeting regulatory requirements and gaining regulatory approval, they will never see the fruit of their labour (Shimasaki, 2009b). A thorough understanding of the regulatory processes and challenges is vital when charting a development path because this knowledge will impact the developmental strategies and testing decisions along the way (Shimasaki, 2009b). The FDA will only conclude a drug is safe and effective for an intended use when the evidence demonstrates adequate and well-controlled investigations, by experts qualified in scientific training and experience to evaluate the effectiveness of the drugs involved (Milani & Pathak, 2018).

There have been numerous attempts to bring botanical drugs to the market through FDA approval, with over 800 IND applications received by the FDA since 1984 (Wright, 2021; Wu et al., 2020). Following the FDA's release of the 2016 BDDGI, there has been an increase in interest towards botanical drug development by the FDA, with over 400 IND application approvals since the BDDGI's release (Wright, 2021). Yet despite the large number of IND application approvals, at the time of writing only a total of three applications have progressed through the NDA stage of development as previously discussed; Veregen, Mytesi and Epidiolex (Wright, 2021; Wu et al., 2020).

Unlike single molecule drugs that deal with anomalies in specific cells, tissues or organs, most botanical products are perceived to lack scientific rigor and are considered holistic approaches to dealing with health ailments (Liu & Wang, 2008). For botanical drug products to achieve market growth and become more acceptable in the US pharmaceutical market, solid scientific evidence is needed to bolster the functionality of the claims for many botanical products (Liu & Wang, 2008; Sun & Qian, 2021). However, this is difficult to do when firms are faced with the challenges of variable sources of botanical raw materials, undefined active ingredients, unclear mechanisms of action, difficulties in safety evaluation, and lack of standardisation due to inconsistent quality and batch to batch consistency (Liu & Wang, 2008; Milani & Pathak, 2018; Sun & Qian, 2021; Tamayo & Hoffman, 2017; Wu et al., 2020; Zhang et al., 2011).

In the USA, botanical drugs must meet the same developmental standards which are applied to conventional small molecule drugs; however, they may do so by providing somewhat different information (FDA et al., 2016; Hoffman, 2015; S. L. Lee, 2019). Regulatory developmental comparisons are shown in Table 5, but it should be noted that these differ on a case-by-case basis (Hoffman, 2015). Nevertheless, the regulatory intent is not to create a separate therapeutic category for botanical drugs, rather to ensure that there is the same level of confidence in their safety, quality, and clinical impact as for conventional pharmaceutical drug products (Dou et al., 2019).

Characteristics	Botanical Drug	Conventional Drug
Chemical Composition	Complex/ heterogenous/ polymolecular	Single molecule
Active pharmaceutical ingredient	Multiple active ingredients with varying levels of activity are possible	Single active ingredient
Characterisation	Varied	High
Control	Process controlled	End product controlled
Source materials	Dedicated sourcing following GACPs	May not require dedicated sourcing
Dosage / Route of administration / Schedule	May already exist (prior human use)	Based on preclinical testing
Predictors of efficacy	Clinical (prior human use)	Preclinical testing
Knowledge of mechanism of action	Rarely	Often
Preclinical toxicity testing	Depends on prior human use	Prior to any clinical trials
Pharmacokinetics	Depends on prior human use and the product	Required
Clinical target	Polymorphic / network pharmacology	Single receptor
Patent protection	Sometimes	Generally

Table 5: Characteristics of botanical and conventional drugs, adapted from Hoffman (2005) and FDA (2016).

The development of a new botanical drug (like that of a conventional drug) invokes the IND and NDA regulations (U.S. Congress, 1934). The approval of an IND submission is considered the formal starting

point of the regulatory process during botanical drug development, as, like for conventional drugs, its approval is required for a botanical drug to undergo testing in human participants (Ciociola et al., 2014; Tamayo & Hoffman, 2017). Furthermore, the approval of the FDA IND application also enables the botanical drug sponsor to begin conducting clinical studies across state lines, as it allows the movement of an unapproved drug product across federal territories (Darrow et al., 2020). The NDA represents the compilation of all data gathered during clinical trials while under IND and any other sources, to support the legal requirements of drug approval and for the drug product to enter the market (CFR - Code of Federal Regulations Title 21, 2021; Darrow et al., 2020; Hoffman, 2015).

As depicted by Hoffman (2015), the IND process can be represented as a three-legged stool (see Figure 8), where each leg represents a key section of the filing making up the IND process prior to the NDA. The *Chemistry, manufacturing and controls* leg defines the drug product and how it is made; the *Preclinical data* leg represents the pharmacology, pharmacokinetics, and the *in vitro* and *in vivo* animal studies for toxicity; and the *Clinical data* leg represents the in-human phase 1-3 studies used to define safety, efficacy, dosage, route of administration and the schedule of the drug product (Hoffman, 2015). Within each of the legs of Hoffman's three-legged stool of the IND application, there are regulatory elements which are uniquely challenging in botanical drug development and have been brought into the spotlight within the literature. These are discussed further below.

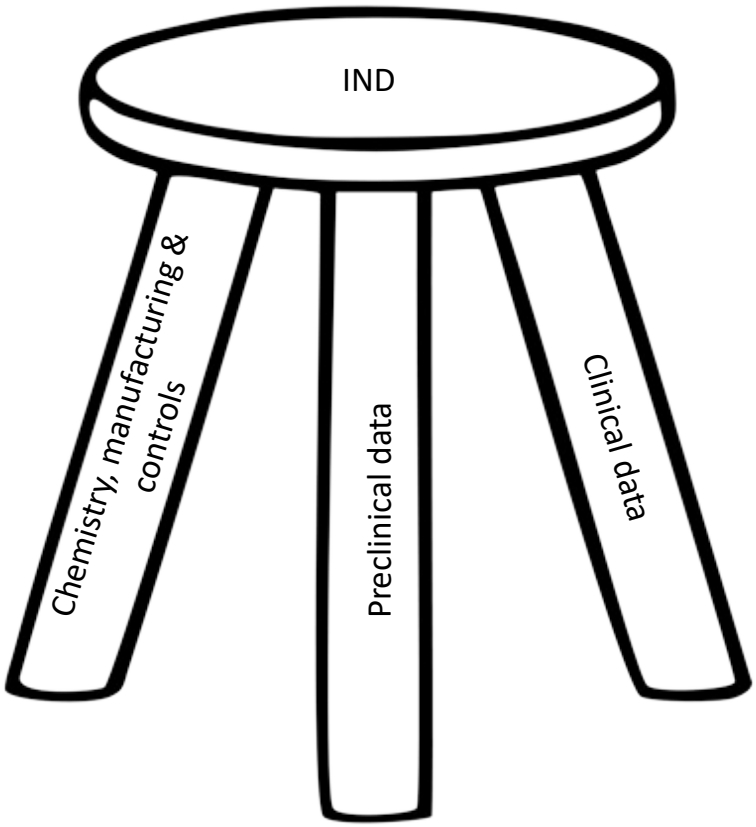

Figure 8: The three-legged stool of IND application during drug development, adapted from Hoffman (2015).

3.2.3.1 Chemistry, manufacturing, and controls

To gain FDA approval, an investigational new botanical drug product must demonstrate safety, efficacy, and quality (Hoffman, 2015). This includes information about the drug product such as chemical identity, stability, purity, and potency, which translates to batch-batch consistency, clinical reproducibility, and standardisation of the botanical drug product – all of which can be challenging in botanical drug development (Hoffman, 2015; Lee, 2019; Tamayo & Hoffman, 2017; Wu et al., 2020). Akin to conventional small molecule drug development, all source materials and chemicals used during the product manufacturing process must be documented (Hoffman, 2015). For botanical drug development, this must also include information about the origin of botanical raw materials, such as the genus and species of the botanical, the location where the plant material came from and the site it was cultivated (Hoffman, 2015; Wu et al., 2020). Furthermore, the manufacturing facility producing the drug products must meet design, qualification, operational and maintenance standards, otherwise known as Current Good Manufacturing Practices (CGMP) (Hoffman, 2015).

The FDA ensures the quality of drug products by monitoring manufacturers' compliance with its CGMP minimum requirements for the methods, facilities and controls used in the manufacturing, processing, and packing of the drug products (Hoffman, 2015). Compliance is upheld and monitored through audited inspections of a range of facilities in the drug supply chain, including manufacturing plants, cultivators, and laboratories (Ohanian, 2016). Such inspections are carried out by both FDA auditors and recognised third party auditors on behalf of the FDA (Lincoln, 2012). Drug products which are intended for the US market but manufactured overseas are not exempt from these inspections. (Ohanian, 2016).

In addition to CGMP, botanical drug sponsors should consider the availability and supply of the source botanical material of interest (FDA et al., 2016; Hoffman, 2015). Source botanical materials should conform to Good Agricultural and Collection Practices (GACPs) support the local communities and environment and take into consideration the local laws and treaties where the source botanical materials are grown (Hoffman, 2015; WHO, 2003; Tamayo & Hoffman, 2017).

By definition, a botanical drug substance contains more than one molecular constituent (Hoffman, 2015). As stated by Checo et al. (2019), Hoffman (2015) and Lee (2015), maintaining quality control and batch to batch consistency is difficult to achieve with botanical drugs, based on their complex polymolecular nature which exhibit natural variations in constituent concentrations. These constituents are generally isolated and unidentifiable, not chemically defined and lack characterisation of full spectrum biological activity (Milani & Pathak, 2018; Tamayo & Hoffman, 2017). The biochemically diverse makeup of botanicals can also contain constituents which may be identified as an active component for one effect, but be considered inactive for another (FDA et al., 2016). Furthermore, a seemly inactive constituent may indirectly contribute to the overall therapeutic effect of the botanical through modulation of the active(s), further adding to the difficulty of characterisation of these drugs (Donno et al., 2016; FDA et al., 2016; Hoffman, 2015). These factors combined make standardisation, which is required to ensure product safety, very difficult.

Another major standardisation issue faced by botanical drug sponsors, highlighted by Tamayo & Hoffman (2017), is the differences in strength and potency of the constituents of raw botanical materials. While raw botanical materials can be derived from the same species, they may contain impurities which are the result of differences in geolocation, harvesting, extraction and processing

methods and the parts of the botanical that are used (Milani & Pathak, 2018; Tamayo & Hoffman, 2017; Zhang et al., 2011). To circumnavigate the documented characterisation and standardisation difficulties associated with botanical drugs, since 2016, the FDA has allowed the "active" to be considered as botanical drug substance as a whole (Hoffman, 2015; Wu et al., 2020). By enabling the whole compound to be considered an "active", whole compound characterisation methods such as chromatographic fingerprinting analysis may be implemented to characterise the drug profile (Donno et al., 2016). Although, the sponsor is still expected to evaluate the current and emerging technologies to enable adequate identification and quantification of the active chemical constituents within a botanical drug where applicable (FDA et al., 2016).

3.2.3.2 Preclinical data

The nonclinical, or 'preclinical' data leg of the three-legged IND stool addresses the early safety questions which cannot be easily assessed in humans (Hoffman, 2015; Wu et al., 2000). These studies consist of a range of *in vitro* and *in vivo* animal studies which are highlighted in Table 6.

A survey conducted by Wu et al. (2000) on botanical INDs received by the FDA uncovered that one third of applications were put on hold and required further regulatory guidance to be accepted. Furthermore, 81% of the submissions placed on hold were found to be deficient in preclinical pharmacology/toxicology information (Wu et al., 2000). Ahn (2017) attributes the preclinical difficulties faced by sponsors, especially non-US based sponsors, to the lack of international harmonisation of regulatory requirements for botanical drugs. Sponsors who have no prior experience in drug development for the US market may not be aware of the differences between the US and foreign market requirements for botanical drugs. Furthermore, some sponsors do not realise that the US regulations require raw preclinical data (as highlighted in Table 6) and not literature information summaries and expert opinion (Ahn, 2017). For these reasons, Wu et al. (2020) advises that sponsors engage in early communication with the FDA prior to the filing of the IND application to enable negotiations on the amount and type of data necessary to initiate in-human clinical trials under an IND (FDA et al., 2016; Hoffman, 2015; Wu et al., 2020).

The active constituents and the mechanisms by which a botanical drug exerts its physiological effects may be unknown or ill-defined due to chemical complexity, making pharmacokinetic and pharmacologic testing infeasible (Hoffman, 2015). Such testing can be waived by the FDA in these cases where mechanisms and constituents cannot be identified, but in the absence of such testing it is difficult to determine drug wash out periods and study the possible drug-drug interactions (Hoffman, 2015).

The amount of preclinical data required is based on the sponsor's ability to provide documentation of prior human use and safety of botanical ingredients sold as dietary supplements or as botanical drugs in other jurisdictions (Hoffman, 2015). Although the use of such data is highly dependent on the route by which the new botanical drug is administered (FDA et al., 2016; Hoffman, 2015). Safety data derived from prior human use becomes irrelevant and generation of new preclinical safety data becomes especially important when botanical drugs products are developed with new dosages, new routes of administration, new formulations, and new indications (FDA et al., 2016; Hoffman, 2015; Lee, 2015; Wu et al., 2020). Furthermore, previous human experience alone does not fulfil the safety requirements for therapies for chronic conditions such as cancer and HIV/AIDS (Milani & Pathak, 2018). Depending on the product, the route of administration and the possible biological effects, the FDA may require additional *in vivo* and *in vitro* preclinical studies. Such examples include botanical drugs which are intended to be applied topically to require skin sensitivity studies, while botanical drugs developed for paediatric or child-bearing populations are required to undergo reproductive and developmental toxicity studies (Dou et al., 2019a; Hoffman, 2015).

Testing	*In Vitro*	*In Vivo*	Information
Mutagenicity	✓		Standard testing for new food, dietary and drug ingredients
Genotoxicity	✓	✓	Standard testing for new food, dietary and drug ingredients
Clastogenicity	✓		Standard testing for new food, dietary and drug ingredients
Acute Toxicity		✓	Required if there is no prior human use or new intended use (<7 days)
Subacute Acute Toxicity		✓	For intended use up to 28 days
Subchronic Toxicity		✓	For intended use up to 3 months
Chronic Toxicity		✓	For intended use over 3 months
Reproductive and Developmental Toxicity		✓	For paediatric and child bearing populations
Carcinogenicity		✓	Depends on ingredient safety
Specialty testing	✓	✓	Specific testing for specific routes, special purpose and specific target organs/ tissues
Pharmacology / Pharmacokinetics	✓	✓	Not always feasible

Table 6: Preclinical testing comparison of small molecule and botanical drugs., adapted from Hoffman (2005) and FDA (2016).

3.2.3.3 Clinical data

Before starting in-human clinical studies, protocols alongside other key documentation (CMC data and preclinical data) must be submitted by the sponsor to the FDA for review and discussion. A development program for a botanical drug product would generally not differ in clinical study design and implementation from that of any drug for the same intended use (FDA et al., 2016; Wu et al., 2020). Although, there is currently no consensus on how to accommodate the complexity of botanical drug products when conducting clinical trials, as effective botanical drug clinical trial design is impeded by the sparse information available due to low number of approvals by Western regulatory agencies (Milani & Pathak, 2018; Sun & Qian, 2021). For study results to be interpretable the clinical studies must be well designed with each clinical protocol fully describing the human populations of interest, with standard

outcome measures assessed through substantiated means, and designed with controls and planned analyses (Dou et al., 2019a; Hoffman, 2015).

Unlike conventional single molecule drugs which have no prior human experience to leverage upon, investigators of botanical drugs have more flexibility within the drug development program for the timing and sequence of phase 1 trials (Dou et al., 2019a). This flexibility comes from previously marketed botanicals with well documented human experience, resulting in typical phase 1 study for a new molecular entity not being required (Dou et al., 2019a; Wu et al., 2020). Sponsors developing a botanical drug who are leveraging safety data from previous human experience may choose to skip phase 1 trials and initiate in phase 2 controlled trials in patients in order to gain preliminary evidence of efficacy of the botanical drug candidate (Dou et al., 2019a). This does, however, require dosage and route of administration of the botanical drug to be the same as the existing human experience and therefore is not applicable to novel dosages, routes of administration and indications for new botanical drugs products (Dou et al., 2019a; FDA et al., 2016). Previous human use may initially be beneficial to firms, allowing faster roll-out of later phase clinical trials. However, many sponsors are still confused by the guidance of the FDA as phase 1 safety data may still be required for NDA approval should the FDA request further safety information during the NDA review process (Liu & Wang, 2008; Milani & Pathak, 2018). As warned by Dou et al. (2019), should firms strategize to leverage previous human experience, they risk creating further financial strains and place uncertainty on the validity of data obtained during phase 2 and phase 3 trials should the FDA request more safety information later in development.

Ahn (2017) argues that the single most common reason that new drug candidates, including botanical drugs, fail to reach the stage of NDA is due to the failure to submit statistically meaningful clinical evidence. For many firms attempting to progress a traditional medicine through the FDA pathway, the challenge of deriving clinically meaningful evidence is exacerbated by the difficulty in transforming individual and traditional experience into transparent, auditable, and reproducible data to support regulatory approval (Sun & Qian, 2021). There are several reoccurring reasons within the literature as to why clinically meaningful data is difficult to obtain in botanical drug development. Some of these reasons are not specifically unique to botanical drugs but are common in botanical drug development, such as insufficient sample size, testing poorly defined illnesses with inaccurate endpoints, heterogeneous study groups due to ill-defined enrolment criteria, high dropout rates and inadequate

follow-ups (Dou et al., 2019b; Liu & Wang, 2008; Milani & Pathak, 2018; Sun & Qian, 2021; Zhang et al., 2011).

Sun & Qian (2021) highlight that when investigating botanical drugs within unknown active ingredients, determining the appropriate inclusion and exclusion criteria and trial size is difficult. Randomised, double-blind placebo-controlled trials are considered the gold standard for classes of medicine by the FDA (Patwardhan & Gautam, 2005). Botanical drugs are difficult to blind as many pose a characteristic or smell that is difficult to simulate without using the active ingredients themselves (Liu & Wang, 2008). For this reason, botanical trials in China have employed positive controls using other known therapeutics in treatment groups to circumnavigate blinding issues, a contrast to the FDA gold standard but possibly an innovation to conventional regulations and thinking (Yuan & Lin, 2000).

3.2.4 Literature gap

This literature review identified a clear gap in the literature for research on management strategy in the botanical drug development space. Management strategy research is largely focused on the industry level, rather than the firm level, making it difficult for firm managers to draw practical guidance or insights. Furthermore, there has been little focus on firms developing botanical drugs, and as this review has elucidated, these firms may face different challenges to firms developing conventional, synthetic drugs for FDA approval. Hence there is a striking gap which this thesis will aim to contribute, by uncovering what the major regulatory challenges are for firms developing botanical drugs and how these firms should strategize to satisfy regulations when attempting to gain US FDA market approval.

Chapter 4: Methods

The following chapter outlines the methodology used to answer the research question:

> *What are the major regulatory challenges faced by firms during botanical drug development, and how do firms strategize to satisfy regulations when attempting to gain US FDA market approval?*

To answer the research question, three sub-questions will be addressed in the research and data collection phase of the research:

What are the major regulatory challenges in botanical drug development?
How do firms strategize to satisfy the FDA regulatory requirements, and specifically, how do the major regulatory challenges identified in this thesis influence or alter how firms strategize during botanical drug development?
How do firms minimise risk during botanical drug development, and specifically, how do firms minimise risk associated with these major challenges?

To answer these sub-questions, an inductive exploratory qualitative research approach using a multiple case study methodology was used. Three cases were generated, drawing upon in-depth semi-structured interviews and a range of different secondary data sources of evidence, before cross case analysis was performed.

This study aims to uncover shared regulatory challenges and the firm management strategies used in the development of a botanical drug candidate following the FDA botanical drug pathway.

4.1 Epistemological perspective

Epistemology is the study of knowledge (Moon & Blackman, 2014). Epistemology is concerned with all aspects of the validity, scope, methods and beliefs when acquiring knowledge (Moon & Blackman, 2014). An epistemological perspective provides a framework for predicting, describing, empowering and deconstructing population specific worldviews (Hautly, 2019; Merriam, 2009). Furthermore, it enhances the knowledge that leads to an increased understanding of the purpose behind qualitative research

(Merriam, 2009). In order for readers to critique research and the methods behind the research, it is important that they understand the epistemological perspective.

An inductive exploratory approach was chosen due to the lack of existing research examining risk mitigation and strategic decision making in the context of botanical drug development for the US market (Merriam, 2009).

After performing a rigorous review of the strategic, risk mitigation, regulation and FDA oriented botanical drug literature, the research was initiated and performed through a constructivist/ interpretivist view. A constructivist/ interpretivist research approach is designed to study the multiple unique realities, descriptions, and experiences of populations (Merriam, 2009). The primary objective was to gather information on each firm's worldview, using open ended questions with no right or wrong answers in conjunction with secondary data to generate unique cases and frameworks on the process of how each firm approached the development of their botanical drug.

Epistemological perspectives in research influence how researchers frame their methodology in the attempt to discover knowledge (Roots, 2007). This is due to certain perspectives and viewpoints being better suited for certain methodologies. The research was approached in an inductive qualitative manner, due to identified gaps within the literature, lack of hypothesized research outcomes and the epistemological perspective outlined.

4.2 Study design

Three methods have been used in this study: company benchmarking, multiple case study analysis and in-depth semi-structured interviews.

Company benchmarking enabled the identification of leads for inclusion in the present research. Firms were benchmarked through publicly available information which was later utilised in the building of case studies and semi-structured interviews. A multiple case study research method was the design chosen to guide this research for two reasons. Firstly, the broad aim of this research is to understand "how" firms developing botanical drug candidates have strategized to satisfy the regulations set in place by the US FDA. Many scholars within the literature have cited case study research as a useful research design in

providing answers to “how” and “why” questions, especially when there is little previous literature (Eisenhardt, 1989; Rowley, 2002; Yin, 2009).

Secondly, the primary aim of this research is to understand the major regulatory challenges faced by firms during botanical drug development. This requires the need to understand each firm’s individual and unique experience during the development of their botanical drug candidate and the conditions of the environment in which the firm exists. This was achieved using semi-structured interviews, where informants were able to provide in-depth information through open ended questions during a one-hour call using Zoom software.

Case studies are effective in allowing researchers to study phenomena unique to each case (Stake, 1995). For this reason, a case study research design was selected for this thesis. Case studies are a valuable way of looking at the world, as they allow researchers to investigate a contemporary phenomenon within its real-life context (Rowley, 2002). Furthermore, Stake (1995) affirms that the primary use of case study research is to synthesise theories and knowledge of a particular subject matter. Ultimately, the objective of this study is to both identify key regulatory challenges and accumulate data to understand risk mitigation and strategic planning processes utilised by firms undergoing US FDA botanical drug development. The knowledge from this study can then be used to guide and inform firms in their decision-making processes.

A multiple case study design was chosen because it enables the identification of replications and trends that occur across cases that would otherwise not be possible to identify in single case studies (Yin, 2009). Multiple case studies are useful when a typical case does not exist for the sample of interest (Yin, 2009). This is certainly true with firms looking to develop botanical drugs. There is great variation between firms in the biotechnology and pharmaceutical industry as firms differ in a range of variables such as the technology in development, regulatory requirements, management experience and capital structuring. Within the varying characteristics between firms, multiple case study design allows for the research question to be addressed, where each additional case study may fill gaps in areas where previous cases may be deficient. Furthermore, multiple case studies can provide greater richness from research findings though triangulation of cases, revealing commonalities and differences (Stavros & Westberg, 2009). Thus, improving the ability of the case study data to be used in generalisation and theory building, thereby increasing the construct validity of the research (Eisenhardt, 1989).

4.3 Company benchmarking

To better understand major regulatory challenges and firm strategy used during botanical drug development, secondary research analysis was incorporated into the study design. The secondary data was obtained by identifying, studying, and 'benchmarking' different botanical firms with the intention of extracting meaningful insights into the progress of their regulatory journey. This data collection method allowed for identification and grading of different firms based on three factors: the stage of development of the botanical drug candidate, the firm's activity and goals, and corporate information of senior management. This grading helped identify and rank firms for inclusion in the current research.

Secondary data inclusion is a validated method of choice as the data obtained for organisations of interest is less intrusive in nature, less time consuming and expensive to gather, and allows for broad geographical region and sample size to be covered over other primary data collection methods (Vartanian, 2010).

4.3.1 Population of interest

There were three populations of interest for this study, all of which were in the biotechnology and pharmaceutical industry. First, firms who have gained US FDA marketing approval, having successfully developed a botanical drug for the US market. Second, firms who currently have a botanical drug candidate in development with the FDA but are yet to achieve marketing approval. Finally, firms who have failed to successfully gain marketing approval for their botanical drug candidate from the FDA. Firms were analysed internationally for inclusion in the population of interest. A global perspective was essential as there are a very limited number of firms in the Australia and New Zealand region who are involved in FDA botanical drug development.

For each firm in the company benchmarking list, the key people of interest who would be suitable for semi-structured interviews were identified. The criteria for inclusion as a key person of interest consisted of senior management positions within the firm, founders, project managers and regulatory affairs employees, as these are key persons involved in the FDA drug development process (Jekunen, 2014).

4.3.2 Data sources and selection criteria

The internet allows access to a plethora of freely accessible information. Firms use their websites to inform potential customers and investors about their commercial activities while others use their platforms to discuss industry trends, release documentation and discuss news articles (Best & Krueger, 2004). The internet proves a good source of secondary data as it is generally high in representative quality of the organisation, easy to access and is ideal in the collection of large data samples when faced with time constraints (Benfield & Szlemko, 2006; Best & Krueger, 2004).

For a firm to be included in the benchmarking list, it had to be a sponsor of a botanical drug being developed for the US market through the FDA botanical drug route and/or be linked to a botanical drug through either their website or media articles. Firms were primarily identified via Clinicaltrials.gov website, using the key search term 'botanical' to search for sponsors of botanical drug trials. Only trials using drugs as the intervention were included in the search. All dietary supplement trials were excluded. The second method of identifying firms for benchmarking occurred through Google search engine and Google Scholar using key search terms 'botanical drug/ US FDA botanical drug/ botanical drug development/ biotechnology botanical drug/ pharmaceutical botanical drug'. A third method of identification of firms occurred through purposive snowballing, where firms were added to the company benchmarking list retrospectively after semi-structured interviews, on the recommendation of informants.

Once a firm with a botanical drug candidate was identified, all data was systematically accessed using the Google search engine. Information surrounding each firm's description, activity status, botanical drug description, stage of drug development, key persons of interest, incorporation date and previous approval history (botanical or other) was recorded via searches utilising publicly available data including the sponsor's name/ botanical drug candidate's name and a number of keyword searches including 'drug/ sponsor/ botanical drug/ US FDA/ FDA botanical drug/ trials /phase 1/ phase 2/ phase 3' or a combination of those terms.

Key people of interest were approached via a cold outreach through LinkedIn, email contact or via their firm's generic company email. This thesis followed a level of 'planned opportunism' as highlighted by Pettigrew (1990), in obtaining primary data samples. This planned opportunism involved using all opportunities available within the time constraints of the research to select cases when the opportunity

to do so was available. This included purposive snowballing sampling with companies who responded to the outreach emails. Purposive snowballing sampling provides the generation of contacts and referrals to other firms and the key people of interest within them (Etikan & Bala, 2017). The use if purposive snowball sampling led to the identification of a greater generation of case firms.

4.3.3 Data management and data analysis

All data gathered through company benchmarking was stored on an excel spreadsheet where key firm information was recorded into categories as depicted by the hypothetical exemplar firm within Table 7. Firm names, informants and collaborators have been withheld throughout this thesis to maintain anonymity, based on the wishes of the informants and the ethics approval received by the University of Auckland Human Participants Ethics Committee, for conducting this research.

Company	Company Activity	Incorporation Date	Company Description	Botanical Drug Candidate	Botanical Drug Description	Botanical Drug Stage	People of Interest	Previous Approvals	Website Link	Priority Rating
Botanico	Currently active	2008	Mexican biotech company developing cancer therapies from plants	BOT144	Extract from *Agave geminiflora* flower used in the treatment of non-small cell lung cancer	Phase IIb	John Smith (J.Smith@Agave.com)	None	www.botanico.com	1

Table 7: Table of company benchmarking criterion which were filled using publicly available secondary data. An exemplar firm has been included.

A list of 28 potential botanical drug firms were identified. The list of benchmarked firms were then assigned a rank of high interest (1), moderate interest (2) or low interest (3).
Firms were benchmarked on the ease of contact, availability of public information on senior management and the amount of information available on the firm and botanical drug candidate. A total of 21 firms of high (1) and moderate (2) interest were then approached for inclusion in the research via semi-structured interviews.

4.4 Semi-structured interviews

Semi-structured interviews are an effective method of primary data collection in exploratory research, where the objective is to ask open-ended questions and collect qualitative data (DeJonckheere & Vaughn, 2019). Semi-structured interviews allow the informant to delve deep within a topic and provide thoughts, feeling and beliefs without being constricted by a rigorous structured interview (DeJonckheere & Vaughn, 2019).

Semi-structured interviews were used to provide information on specific regulatory challenges unique to each firm. Additionally, these interviews also provided insight into how firms minimise risk and strategize their approach in development of their botanical drug candidate. In-depth semi-structured interviews were used as the primary information gathering tool within each case.

The semi-structured interviews were based on pre-written questions which were developed through emergent themes identified in the analysis of the literature. The interviewer had a broad understanding of the topics and questions which were discussed, but there were no expected or preconceived responses from each informant. Review of the relevant botanical drug development, commercial strategy and risk mitigation literature had outlined general key questions to be considered when interviewing informants. There was no expectation that informants would discuss any of the information or theories during the interviews that was found within the literature.

Interviews were conducted via Zoom software and were recorded with permission of the informants. Recordings were transcribed for further analysis and the informants were given the opportunity to review, retract and change any information post interview. To ensure the validity of the interview, it was important that the informant's opinions were reflected as accurately as possible. The interviewer remained neutral during the interview minimising threats to data validity by not sharing any preconceptions on the subject matters and avoiding leading questions. The questions were unguided, allowing the informant to elaborate on areas in which they deemed to be important (DeJonckheere & Vaughn, 2019).

Informed consent is an important ethical consideration due to the commercial sensitivity of some of the documentation and information gathered during the interviews. Informants were provided ethical

consent forms which were signed and returned prior to interview. These forms highlighted the aims, purpose, and nature of the study, and how the study data would be collected and stored.

4.5 Case study research

To understand firm management and the major regulatory challenges during botanical drug development, multiple case study analysis was conducted. The multiple case study analysis included in-depth semi-structured interviews, and a range of secondary data sources including podcast interviews.

Case study research provides distinctive means of developing theory by using in-depth insights of empirical phenomena within their specific contexts (Eisenhardt, 1989). Botanical drug regulatory requirements can differ greatly due to varying levels of botanical complexity unique to each drug. Therefore, each firm may not face the same regulatory challenges, thus changing their risk mitigation tactics and firm strategy. For these reasons, a multiple case study methodology was adopted as it addresses the hurdles associated with investigating the regulatory challenges and firm management characteristics of a highly technical field (biopharmaceutical drug development).

The inclusion of multiple case studies allows investigation of a broader range of behavioural and case specific understandings (Yin, 2009). This enables a generalisation based on inter-case recurrent themes and provides a more convincing argument for emergent theories from the research since the data is based on several different resources (Yin, 2009). Since this research is based on three specific variables; regulatory challenges, firm strategy and firm risk mitigation, the triangulation of multiple cases will provide greater validity to the results of this study (Siggelkow, 2007; Stavros & Westberg, 2009).

The case study sample included in this study consisted of three biotechnology firms. Due to time constraints and the length of time it took for firms to respond to interview requests, the case study sample was limited to three. As Hine & David (2007) have found, the accepted range of case study sample size to generate informative findings falls between two to four cases. Each case study included had a botanical drug candidate in different life-cycle stage with the US FDA. One had failed to make it to market, the second was still in development and the third was successful and is now on the market in the US.

Multiple case studies were built to provide information on how each firm operated in their specific environment. Each case was built around a single firm and the associated botanical drug in which the firm was developing, failed to develop, or successfully developed for the US market. Understanding the science and production requirements of each case's botanical drug candidate provided insight into how the regulatory challenges affected its development. Subsequently, obtaining data about how each firm mitigated risk, developed strategies, and dealt with unique regulatory challenges, helps generate concepts in botanical drug development. The multiple case study approach increases the transferability of the findings of this research allowing for development of conceptual models and theory building (Stavros & Westberg, 2009).

4.5.1 Podcast data

In-depth semi-structured interviews were not the only interview data source used for the generation of data within this thesis. Podcast interviews with key informants discussing the development of their firm's botanical drug candidate were also included.

Podcasts are an effective digital medium for research communication, professional education and can be used as a method for data collection (Eringfeld, 2021; Malecki et al., 2019). Typically, there is a pull for leaders in their fields to speak on their topics of expertise, and therefore podcasts can provide researchers with good sources of information from interviews and focus groups as they elicit rich, detailed, and affective responses from participants (Eringfeld, 2021).

Where available, podcast interviews were included as additional data sources within this research. Three podcast interviews with members of senior management at a biotechnology firm were used in case C, alongside several secondary data sources for triangulation of information. The podcast interviews consisted of in-depth unscripted interviews where relevant information surrounding the development, production and manufacturing of the firm's botanical drug was discussed. The questions and discussions within the podcasts had a high relevance and a large degree of crossover with the current research topic. Therefore, the information provided within these podcasts was able to implicitly and explicitly answer many of the pre-written semi-structured interview questions used in gathering primary data. Furthermore, the seniority of the informant speaking within each podcast interview and

the educational and academic nature of each of the podcast shows legitimises the high-quality data collected from the podcasts.

4.5.2 Secondary data

Secondary data was collected to help illuminate the context and development history of each case study with any relevant information that was not discussed within the semi-structured interviews. Understanding the context of each firm is essential to understanding the strategic and risk mitigation decisions made by key decision makers within each firm (Reynoso, 2010). Therefore, the collection of secondary data that delivers insights into the context of each firm is an important part of building a cohesive and representative case. Secondary data was gathered for each case pre- and post-semi-structured interview.

Secondary data helped inform cases by influencing key questions to be addressed when conducting semi-structured interviews. The secondary data outlined information unique to each case, such as regulatory requirements that the firm may or may not have struggled with, facilitating deeper insights to be developed during interviews.

The majority of the secondary data was obtained through the internet via publicly accessible databases, company websites and forums. The publicly available secondary data consisted of several regulatory reports and communications, firm reports, secondary interviews with key stakeholders, media reports and information from government and commercial databases. As previously discussed, these data sources were accessed via Google searches using the names of botanical drug and firm in conjunction with keywords described above in 4.3.2.

Two of three cases included in this study provided commercially sensitive documents not available in the public domain to be used as secondary data sources. These documents were provided under good-will following post semi-structured interviews. The documents were analysed and incorporated into the research results. The commercially sensitive secondary data sources included business plans, investment presentations, meeting minutes and consultant guidance documents.

4.5.3 Data storage

The company benchmarking Excel spreadsheet and all primary and secondary data were downloaded and saved within a password protected cloud database, dedicated only to the storage of the data for this study. Each case had its own folder which contained in-depth semi-structured interview recordings and transcripts. All secondary data sources relevant to each case and any additional data sources such as podcast audio recordings and transcripts were also stored in their respective case folders. Due to the confidential nature of the data, only the author of this study had direct access to this data.

4.6 Data analysis

Recorded interviews were replayed, and transcripts were analysed alongside to ensure that all auto-transcriptions generated by Zoom were true to what the informant disclosed during their semi-structured interview. The author of this study corrected any mis-transcriptions this way. Primary and secondary data sources were read multiple times to increase author-familiarity with the data and to identify initial codes from themes within the data, prior to thematic analysis.

Data analysis was conducted through a qualitative research analytical software, Nvivo, access to which was provided through the University of Auckland. Thematic analysis was undertaken in a hierarchical coding order, first conducted on primary data obtained from the semi-structured interviews, followed by podcasts and other secondary data sources. Thematic analysis goes beyond quantification of data, it is used as a process of identifying, organising and understanding implicit and explicit themes from within qualitative data (Saldana, 2021). As highlighted by Gibbs (2018), coding memos were used to maintain coding definitions and avoid definitional drift. This allowed for consistency during the coding process and creation of sub-codes where required, for the identification of more specific underlying themes within the data (Saldana, 2021).

4.6.1 Triangulation

Triangulation refers to the use of multiple methods or data sources in qualitative research to develop a comprehensive understandings of a specific phenomenon (Patton, 1999). Triangulation is also a qualitative research strategy used to increase validity through the convergence of information obtained from different data sources (Carter et al., 2014). Furthermore, triangulation can deepen the researcher's understanding of the topic and thus increase their confidence in the findings from previous literature, and thereby facilitating an increase confidence of the research data (Thurmond, 2001).

Four different triangulation methods are commonly used in qualitative research: method triangulation, investigator triangulation, theory triangulation, and data source triangulation (Patton, 1999; Thurmond, 2001). The data triangulation method was used within this study. This triangulation method was selected due to ease of implementation and the depth of phenomenon exploration facilitated through the inclusion of various secondary data sources.

A total of three cases were built for this study. Each case leverages multiple sources of data providing triangulation to better represent each firm's unique position (Yin, 2009). As previously described, this study followed a level of planned opportunism, where all opportunities available within the time constraints of the research were used as efficiently as possible. Each case within this study was built through the triangulation of different date sources as shown in Table 8.

Case	Data Samples	Data Sources
Firm A	Primary & secondary	Two in-depth semi-structured interviews + publicly available information + commercially sensitive documents
Firm B	Primary & secondary	Two in-depth semi-structured interviews + publicly available information + commercially sensitive documents
Firm C	Secondary only	Three podcast interviews + publicly available information

Table 8: Table of cases and their data sources used in data triangulation.

4.7 Chapter summary

This chapter has outlined the methodological approach taken for this study and the justification of the qualitative approach in relation to the research question. Furthermore the methods used in the collection of primary and secondary data has been described, with an explanation benchmarking selection criteria and the interview technique utilised. Studying botanical drug development with an emphasis on key regulatory challenges and understanding risk mitigation and strategic planning processes is the aim of this study. Through the analysis of multiple real world cases, the data from this thesis may provide a useful resource to help with the creation of an efficient botanical drug development plan for firms seeking to gain FDA botanical drug approval.

Chapter 5: Results

The purpose of this chapter is to report the data obtained during the building of each case from primary and secondary sources. Quotes obtained from firms during in-depth interviews will be integrated throughout this section to provide further depth to each case. Each case will be discussed giving insight into the experience the firm faced during botanical drug development, followed by a comparison of case outcomes and key themes.

5.1 Case study background

A total of three cases were developed using two or more in-depth semi-structured interviews and a number of different secondary data sources. Each case represents individual firms that, at the time of writing, had a different regulatory outcome; failed, ongoing or approved. This section will describe each case providing insights into the regulatory challenges faced and the strategies used during botanical drug development.

5.1.1 Firm A: Failed

Firm A was founded in New Zealand in 2004 as a spin out from a successful nutraceutical dietary supplement company. Firm A was founded with the aim to prove efficacy in a bark based botanical product and develop it into an oral botanical drug for migraine treatment and prevention. The botanical drug candidate was well developed at firm inception, with manufacturing and quality control process in place due to its availability on the market as a dietary supplement.

Firm A successfully raised $1 million in capital promptly after establishing the firm. This funding enabled the development of the botanical drug candidate in preclinical studies and the application and granting of a patent for the methods of treating migraines with plant extracts. The capital also funded the FDA IND application process and enabled research to be conducted with a number of universities and research partners across Australia and New Zealand. Firm A published six research papers on the neurological benefits of its extract, including a peer reviewed paper which was successfully published in the Journal of the American Medical Association (JAMA) on migraine prevention.

Firm A had developed quite a strong position for the development of its botanical drug product based on its IP, research and development strategies. The firm faced regulatory challenges around the initial formulation of its botanical drug candidate and the lack of transparency in what was expected by the FDA, but ultimately did not struggle with regulations. However, due to poor fund management by the initial investors and shareholder disagreements, Firm A ran out of capital and could not engage in further regulatory development of its botanical drug candidate. This led to the senior management moving on to different roles at other firms. Firm A is still a registered company and files each year, but development of its botanical drug candidate has been abandoned. Two in-depth semi-structured interviews were conducted with a single informant, the ex-CEO/ founder of Firm A, who has a strong background in senior management in technical fields.

Firm A had a target market and strategy formed from the day the firm was established. Firm A's goal of FDA approval to gain access to the US market for its botanical drug candidate was based on three factors. First, Firm A's nutraceutical parent company was already on the market in the US with manufacturing and GACPs established. Second, Firm A knew that its ability to raise capital would be higher if it were developing its drug for the US market. Third, the migraine market in the US was identified as the market to generate the biggest return at the time.

> *"Part of it was looking ahead, we knew we would have to raise more capital and that sort of thing, the US is the drug market for that. Also the primary payoff of getting on market is quantumly massive. I have to check facts, but back then I'm pretty sure that even if we got a small percentage of the market we were looking at around the $800 million category." – Firm A*

Firm A's chairman had extensive prior experience with drug development in the US and this knowledge was used to inform Firm A's strategy in relation to the FDA's regulatory requirements. Collaboration through discussions with other botanical drug firms and the FDA via pre-IND meetings were conducted early to mitigate as many risks as possible. For further guidance and to maximise communication during Firm A's limited time with representatives of the FDA, Firm A partnered with a US-based regulatory consulting firm.

> *"They [the consulting firm] had a huge influence on how we were going to approach it [development] because we'd hired the company in California who had real professional*

experience on it [drug development]. So that set out the whole of what we were going to do, and how we were going to approach the FDA and act as the interlocutor with the FDA." – Firm A

The FDA's Botanical Drug Development: Guidance for Industry (BDDGI) draft document was released approximately 18 months prior to Firm A beginning to develop its botanical drug candidate. Firm A found that the BDDGI document was difficult to interpret due to lack of clarity by the FDA. This lack of clarity meant Firm A was unsure whether it could use the previous human use data of the active pharmaceutical ingredient (API) from the on-market nutraceutical product, to enable it to begin phase 1 trials while running a larger formal safety study.

"The challenge with the guidance document was trying to interpret what they [the FDA] were looking for when they were literally only draft guidelines." – Firm A

Regardless of the guidance offered by the BDGGI, or lack thereof, Firm A strategized that the development of its botanical drug candidate were to "*go by the books"* and follow the typical pathway of a small molecule drug. This was possible due to the minimal natural chemical variation in its botanical drug candidate enabling consistent quality in manufacturing.

"From day one we planned it being a drug, and going down the typical drug route as any other drug would. We were developing a botanical drug, but we were going to do everything exactly the same as if we had a [single molecule] drug. Whatever the testing was, whatever the requirements were, we were trying to go along with the FDA to kind of fit into their [small molecule] drug thinking because despite the fact they had the guidelines and stuff, the FDA was still and is still a [small molecule] drug approval company." – Firm A

Firm A was faced with regulatory challenges prior to its safety trials for the original formulation of its botanical drug candidate due to the inclusion of vitamin C as a product stabiliser. Through collaborative early discussions, the FDA concluded that levels of vitamin C within the botanical drug candidate were too high, as these levels were above the recommended daily dietary intake level. Furthermore, as vitamin C is considered an active pharmaceutical ingredient (API), the botanical drug candidate would then be considered a combination therapy and need to be developed as such. This led to Firm A altering its formulation to remove vitamin C before moving into preclinical testing.

As previously mentioned, Firm A did not face any challenges relating to manufacturing and product quality control, due to the procedures and facilities set up through the parent nutraceutical company. As the firm did not make it past the IND stage, it did not face any clinical regulatory challenges.

> *"We had a remarkably consistent product which was unusual. We had HPLC (high performance liquid chromatography) testing and we found early on that if some Douglas fir bark got into the Pinus Radiatus bark, we could detect it without a problem." – Firm A*

Firm A ultimately discontinued the development of its botanical drug candidate when capital resources ran dry. A capital wall was hit when the original venture capitalist was unable to provide further financing due to its fund not being set up for additional investment rounds. Furthermore, the parent nutraceutical company who was the major shareholder of Firm A "*refused to sell their shareholding and were pretty dyed in the wool*". As a majority stake was held by a nutraceutical company who refused to sell, combined with the inability to receive further finance from the original venture capitalist, the firm became a '*red flag'* to additional investors.

> *"We were actually on the right track. But the thing that really crippled us up at the end of the day is [redacted] invested, but when they put their first round together they had no way of carrying on to additional rounds, so when I went out to raise capital for round two they'd [other investors] say well if you've got your original venture fund you'd expect them to come in and keep going.*
>
> *But no - they're out, they can't do it because of their structure. No one in the states could understand that at all. You know we were at a at a dead end right there.*
>
> *Everything was further derailed due to the fact that we still had a very large nutraceutical shareholder who was on the board. And that caused a lot of problems in the capital market as all the investors were geared up for regular drug development. That was the deal killer right there." – Firm A*

Thus, for the informant, Firm A's biggest hurdle was not the regulatory requirements of developing a botanical drug product, but the structure of the company and the capital available.

5.1.2 Firm B: Ongoing

Firm B is a pre-IND stage New Zealand biotechnology company founded in 2017, based on research into the underground stem of a tropical herb plant and its potential therapeutic applications. Firm B was founded with the aim of developing a botanical drug which targets auto-inflammation pathways and can be used to treat conditions such as interstitial cystitis, sepsis, and arthritis. Firm B is still in infancy in terms of available capital and human resources. The firm is currently undergoing its first major capital raising round. The capital raised will facilitate the hiring of required staff and fund further development of its botanical drug candidate through IND and into phase 1 studies. Through knowledge sharing and paid partnerships, Firm B has identified risks and strategized how to approach the development of its botanical drug candidate. Furthermore, Firm B has successfully developed a novel manufacturing process, novel application of biomimicry, novel extraction process, novel composition, and novel application of use for its botanical drug candidate. All these aspects are patented, and Firm B has freedom to operate in the space.

Two in-depth semi-structured interviews were conducted with two informants from Firm B. These informants consisted of the CEO/ founder who has a strong background in ethnobotany and the dietary supplement industry, and the chairman, who has extensive experience in biotechnology commercialisation, the pharmaceutical industry and venture capital.

Prior to beginning development of any botanical drug candidate, Firm B's CEO did extensive research to build a foundation on which the firm is built on. The CEO spent years researching and actively engaging in knowledge sharing and collaboration with a variety of healthcare professionals and researchers across Australia and New Zealand in both the private and academic spheres. The research investigated the APIs contained within the tropical herb, how to maximise extraction of these APIs and the feasibility around clinically proving that it can be used as a therapeutic. Furthermore, consumer and prescriber surveys were conducted to assess the preference of a botanical drug over the current standard of care.

> *"I was mind blown actually, I think around 78% of consumers said they would prefer a natural product over a synthetic drug. Same with doctors, around 70% said they would want to prescribe." – Firm B*

This information enabled Firm B to assess and strategize the pathway forward. The firm decided to target the US market and develop a botanical drug candidate through the FDA because of the specific treatment indications for which the drug can be prescribed, the market size (~$400 million) and the lack of competition in the space. Firm B does aspire to enter other markets, such as the European market, but it believes that by gaining FDA approval first it will have a better chance at entering other markets and will simultaneously generate revenue to fund additional regulatory engagement.

> *"By aspiring to probably the best market in the world, if approved, we think that the FDA will give us the clout to go sideways into other markets." – Firm B*

Firm B acknowledged that it could get its product on the market sooner as a dietary supplement. This is because the tropical herb is a food product and is generally recognised as safe (GRAS). Although, the firm felt that it would be tarnished by other dietary health supplements which are *"untested with bad quality, bad quality controls and mislabelled ingredients"* if it took this route. Additionally, by developing a drug which would be prescribed, Firm B can position itself in a less saturated and more lucrative market. Firm B, however, has not ruled out the possibility of entering the dietary supplement market after gaining US FDA botanical drug approval.

> *"The health conscious consumer does value medically proven products more than dietary supplements." – Firm B*

Firm B has strategized to focus on an initial indication before expanding into the other areas previously mentioned. By targeting interstitial cystitis as the primary indication during development, Firm B has strategized to leverage the rare disease accelerated route, which is a three-year short-cut to market. Once on the market, Firm B aims to run additional trials and expand into other auto-inflammatory indications.

> *"It's a cheeky way to get indications for rare diseases, such as focusing on a certain population of interstitial cystitis with ulceration in the bladder. Then once you get through you just expand into other indications really quick. It's a trick a lot of the pharmaceutical companies have used in the past." – Firm B*

Firm B aims to maximise its regulatory success and minimise risk by collaborating and running all decisions through experienced parties. As the CEO has no previous experience with the FDA or the botanical drug route, several local industry professionals have been assembled as advisors on key decisions which are made by Firm B. Firm B has also partnered with a US based contract research organisation who has extensive experience with the FDA and the botanical drug route. The contract research organisation has primarily been hired to help prepare and oversee the IND application and phase 1 and phase 2 trials.

> *"All of our regulatory pathways will require consultants and we are going to keep minimising risk by getting experience people to advise us." – Firm B*

Firm B is currently in early stages of development of its botanical drug candidate and is relying heavily on the FDA's BDDGI document and its US partner for guidance. The firm has developed methods of standardisation for its candidate and is currently optimising its raw plant material resourcing while working towards good agricultural practices certification. Firm B has expressed frustration in the lack of clarity of the BDDGI document regarding both CMC requirements and safety and toxicology.

> *"Having a little more guidance would be really helpful. There are so many grey areas, it's frustrating to be honest." – Firm B*

Firm B is strategizing to leverage prior human use and the literature of the toxicology on the botanical raw material. The CEO stated that they *"have a really good indication of the safety material through a lot of established peer reviewed research which can be used to support the development of the product".* Although simultaneously stating its fear of whether the FDA may require more safety information in later stages of development and whether these requirements may impact the applicability of earlier studies.

> *"So I looked at other companies taking these pathways in phase 3, where the FDA can come back and say hey you're testing it now on more than 200 people, can I see an animal study on toxicology. It's terrifying, I'll have to budget for it. Doesn't mean it's going to happen.*
> *So things like that are the unknowns, it's frightening." – Firm B*

5.1.3 Firm C: Approved

Firm C is a US based success story in the botanical drug space, with an on-market FDA approved botanical drug indicated for the symptomatic relief of non-infectious diarrhoea in patients who are on antiretroviral therapy. Firm C was founded in 1989 based on ethnobotanical work in South American rainforests. The firm was founded with the aim of translating traditional medicines used by populations throughout South America into clinically proven drugs for the US market, while simultaneously returning value to local communities, ensuring sustainability in resourcing of the raw botanical materials. To date, the firm has conducted 21 clinical trials with its botanical drug in a variety of therapeutic indications.

Firm C's botanical drug candidate was the first oral botanical drug to be approved by the FDA and was initially approved in 2012 through a licensor who was commercialising the firm's IP. It became evident that the licensor had no interest or strength in the AIDS/HIV space and the commercial rights were bought back by Firm C after a lengthy legal dispute. The botanical drug was then renamed, in conjunction with an educational campaign for healthcare professionals, and launched again in April of 2018. Three in-depth semi-structured podcast interviews were conducted with two different informants from Firm C. One interview was conducted with the CEO and two interviews were conducted with the executive vice president.

Due to Firm C being an American firm, the US was the first market of choice. Firm C had previously developed non-pharmaceutical dietary supplement products for diarrhoea but were interested in developing a prescription drug product due to the higher levels of rigor and efficacy behind a pharmaceutical product.

> *"Dietary supplements can of course have great benefit to health and often are accessible to a wide diversity of populations, but pharmaceuticals go through extensive rigorous testing of safety and efficacy required by the FDA and are scrutinized carefully by pharmacologists, toxicologists and GMP specialists in manufacturing. They are quite different." – Firm C*

When the firm first began developing its botanical drug candidate, the FDA botanical drug route did not exist. Firm C originally strategized for its candidate to be developed via the standard FDA drug pathway.

"Ironically there was no botanical drug team prior to 2004 and we started working on this in 1990. As we were moving forward, it was always viewed by us as a new molecular entity. When the botanical drug review guidelines came out, we were viewed as a botanical drug." – Firm C

Firm C focused on multiple partnering strategies from the outset of inception. Each steppingstone during development of the firm's botanical drug strategically leveraged a relationship with an external party. The firm strategized and engaged with bioorganic chemists and natural product experts from around the world during the early characterisation stages of the botanical drug's development.

"We brought scientists from the Philippines, from Ecuador, from Papa New Guiney, from all around the world, to do six-seven month stays with us." – Firm C

Firm C also recognised that its strength was geared towards ethnobotanical drug discovery rather than clinical drug development. After preclinical development of its botanical drug candidate in 2001, the firm mitigated developmental risks by licensing its IP to an experienced third party for further development.

"So what we're all about in this company is risk mitigation. Drug development is all a risk based endeavour." – Firm C

The traditional uses of the raw material of the plant in which Firm C's botanical drug is sourced, is used for a large variety of different ailments by indigenous populations across South America.

"It's used for a variety of things, believe it or not. Orally for coughs and flu, and of course, diarrhoea and GI problems. It's also taken that way [orally] for ulcers.

It's also used for topical wound healing for insect bites, after tooth extractions and vaginal baths. Believe it or not, all are traditional." – Firm C

Firm C decided to focus on one initial indication to get its drug on the market; the treatment of diarrhoea in patients who are on anti-retroviral medications, before expanding into other target areas.

Firm C is currently underway with the expansion of its botanical drug's indications and has gained orphan drug designation by the FDA to fast track the botanical drug to market for short bowel syndrome and congenital diarrhoeal disorders. Furthermore, Firm C is looking into treatment of chemotherapy induced diarrhoea in humans and have recently been approved by the FDA for this indication in dogs.

> *"It's all about the risk mitigation of having five or six additional indications and additional populations, that we could eventually target once they're approved, promoted and educated for. All of which comes from the same drug that has already been approved and is out there on the market right now." – Firm C*

Firm C's CEO explained that the firm mitigated as much regulatory risks as possible during the planning of expansion of its indications. Through two years of collaborative discussions with the cancer and gastrointestinal divisions of the FDA, eventually Firm C and the FDA agreed on pivotal protocols for patient enrolment criteria, and the endpoint definitions and statistics that would be used.

> *"This enabled agreements to be made before we actually started the trials." – Firm C*

Firm C faced a number of regulatory challenges during development of its botanical drug, in particular with its CMC data. Fortunately, through the firm's partnering and reimbursement strategy with the communities from where the product came, Good Agricultural Collection Practices (GACPs) were satisfied early on. Although, Firm C struggled with characterisation due to the botanical drug exhibiting a large degree of uncertainty in its chemical composition.

> *"It was challenging as a lot of the technology available at the time wasn't able to easily identify this complex compound." – Firm C*

Firm C's botanical drug consists of a number of chemical oligomers which proved to be difficult to separate and quantify. Ultimately Firm C satisfied the FDA's characterisation requirements using chromatographic, spectroscopic, spectrometric and acid hydrolysis methods, alongside a clinically relevant bioassay based on the botanical drug's mechanism of action.

"Once it was isolated and identified, my colleagues were able to make up an extraction and purification procedure that produces the same basic mixture of these polyphenols and anthocyanins each time. In a manner that satisfied the US FDA, including the botanical drug team of the FDA." – Firm C

There were also notable challenges with the natural batch to batch API variations, which may have altered the response to the botanical drug when consumed. This challenge was ultimately overcome through the combination of multi-dose phase 3 trials and pharmacology data suggesting that channel saturation occurred at low levels of dosage, and therefore no dose response was observed. This meant that chemical variations observed in different botanical drug batches does not affect the clinical response of the drug as dosing is higher than the minimal saturation level.

Firm C's botanical drug candidate was approved based on the therapeutic consistency and efficacy in clinical trials alongside the development of a bioassay for standardisation of batches. The firm was assigned two post-marketing commitments which included a study to evaluate interaction with other substrates within the gut, and to determine how the botanical drug interacts with specific enzymes and transporters expressed within the gut. Even after approval of its botanical drug, Firm C still faces regulatory challenges to keep it on market for the original indications through the FDA's annual auditing.

"One of the challenges that we face is all this is heavily regulated by the FDA each year. You have to comply with the chemistry, manufacturing controls and specifications, then you have to follow good agricultural and manufacturing practice. These are costly, challenging and heavily technical." – Firm C

5.2 Comparison of Case Studies

Having summarised the three cases included in this study, the purpose of this section is to compare the identified themes obtained from analysis of the data. A total of three case studies were formed using in-depth interviews and secondary data sources. Each case represents a firm that has had or currently has a botanical drug in development with the FDA. Quotes obtained from firms during in-depth interviews will be integrated throughout this section to provide further depth.

Each of the three cases represent a different data population based on the developmental status of its botanical drug: approved, ongoing or failed. Furthermore, each case was developing its botanical drug candidate for different indications, although all via the same route of administration. These are shown in Table 9.

Case	Development status	Target indication	Route of Administration
Firm A	Failed	Migraine prevention	Oral
Firm B	Ongoing	Interstitial cystitis	Oral
Firm C	Approved	Antiretroviral induced diarrhoea	Oral

Table 9: Table of cases, their development status and drug info.

5.3 Regulatory challenges

The purpose of this section is to build a greater understanding of the regulatory challenges faced by cases during the development of their botanical drug candidates. A range of regulatory challenges were identified through the triangulation of data in building each case study. Most challenges identified were shared frustrations across cases and originated early in the development process of the botanical drug candidate.

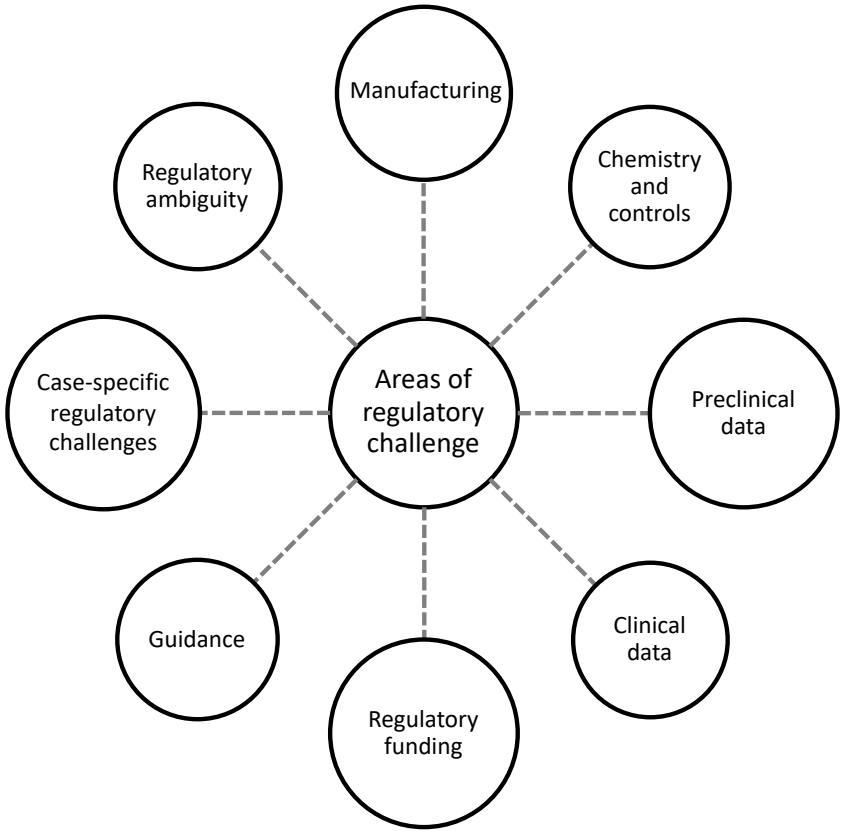

Figure 9: Regulatory challenges perceived by case study firms.

As depicted in Figure 9, the regulatory challenges associated with botanical drug development were related to manufacturing, chemistry and controls, preclinical data and clinical data. Furthermore the ambiguity and funding associated with regulatory development of a botanical drug was also noted across cases. These are each discussed in the following sections.

5.3.1 Chemistry and controls

Two of the three cases faced challenges in the standardisation of their botanical drug candidate during development. The significant challenges for Firm B and Firm C were the lack of adequate controls which lead to variations in the API consistency, unknown mechanisms of action and difficulties with characterisation of all active components within the botanical drug candidate.. Firm A did not experience any difficulties with the standardisation of its botanical drug candidate due to predetermined manufacturing and quality control processes. Furthermore, Firm A's raw botanical materials exhibited high natural consistency, while Firm B and Firm C's raw botanical materials did not. Comments made by informants in each case on each of the identified standardisation challenges are exemplified and contrasted in Table 10.

Case	Challenge	Standardisation
Firm A	No	*"Using HPLC and other methods we could identify if any other components got in. We could pick it up any differences in batch consistencies without a problem"*
Firm B	Yes	*"We have developed a method based on one of the identified main actives and how much of the main active is needed to have an effect in rats. But we don't know how the FDA will respond to this"*
Firm C	Yes	*"Structural elucidation was not easy. It was very challenging at as some of the technology at the time could not easily identify what was in the complex compound"*

Table 10: Table of standardisation challenges.

Firm A also experienced challenges in the stability formulation of its botanical drug candidate early in development after discussions with the FDA. Neither Firm B nor Firm C made any comments on stability associated challenges.

5.3.2 Manufacturing

The importance of standardised manufacturing and raw material resourcing is a repeated theme across all cases. All cases stated the importance of controlled and ethical sourcing of raw plant materials

following GACPs, but only two of the three cases (Firm B and Firm C) found this to be particularly challenging. Within manufacturing there were specific challenges identified. First the varying environment conditions meant it was a challenge to minimise contamination of the raw plant materials. Second, the availability and sustainability of the raw materials to match the requirements of the market.

Firm B felt that achieving good agricultural practices is an unclear and challenging process that is required by the FDA. Firm B highlights that there is a particular challenge with maintaining consistency across all plant matter and ensuring that there are no agricultural products, such as fertilizer residue, which may be detected in the end product. Firm B expressed that it is worried that the challenge is likely to be exacerbated when scaling to market, especially across different cultivation sites.

Firm C understood the importance of GACPs in line with the firm's founding ethnobotanical culture. Planting, reforestation, and support of local communities was a core part of the firm identity from inception which satisfied the FDA's sustainability and availability requirements. However, Firm C acknowledged that obtaining GACPs status was a complex and long process which involved multiple stakeholders to achieve. Firm C overcame contamination difficulties highlighted by Firm B through multiple extraction and purification processes developed over many years, ensuring the end botanical drug consists of the same key botanical components.

> *"Between our two approaches of community supported harvesting and reforestation, we created basically a sustainable management." – Firm C*

Firm A expressed a good understanding of the importance of GACPs and manufacturing processes ensuring chemical consistency. Fortunately Firm A's botanical drug candidate had remarkable chemical consistency which was verified through the extensive manufacturing processes developed by the firm's parent nutraceutical company. Furthermore Firm A stated that it met GACPs as the botanical drug candidate was a by-product of a primary industry which adheres to intensive sustainable forest management policies and produces botanical raw material in excess of what was required for market by the firm. All raw botanical material was sourced from cloned trees that did not exhibit seasonal variation. For these reasons Firm C did not face any specific challenges associated with manufacturing and GACPs.

"All trees were grown to just about the same age and had to go through a barking process and through all those processes we were left with a remarkably consistent product, which was unusual and pleasantly surprising." – Firm A

5.3.3 Preclinical

Preclinical safety data was a challenge for two of three cases. Both Firm A and Firm B expressed frustration with the lack of clarity surrounding previous human use as a surrogate for safety data. In early discussions with the FDA, Firm A was denied leveraging previous human use of dietary supplements containing the same API, due to substantially larger doses of the API planned to be used within the botanical drug candidate. This resulted in Firm A conducting safety trials that would be used for the likes of single molecule drug development.

Firm B planned on leveraging the previous human use of the raw material of its botanical drug candidate, which had GRAS status and history of traditional use. Firm B states that it has expert opinion which is strongly in the favour of using this safety data, but it is a risk that it may need to budget for should the FDA require further data. Firm B also expressed frustration on the *"grey area"* surrounding what the FDA deems to be substantial previous human use and if further safety data will be required later in development.

Due to the infancy of the botanical drug route around the time of Firm C's safety trials, it conducted traditional safety testing and did not attempt to leverage previous human use (as shown in Table 11).

Case	Challenge	Preclinical
Firm A	Yes	After being denied prior human use for safety: *"We ended up doing a very comprehensive two species testing"*
Firm B	Yes	*"You can go through that botanical drug pathway with a dossier of stuff that says that, for this, and this, and this reason it is safe enough, and in paper on the guidelines they will accept that we have seen other drugs go through that hurdle.* *But really it is a judgment call on their behalf, so we're worried about that"*
Firm C	No	*"We conducted all the classic safety studies and then efficacy studies required for any pharmaceutical because as you know, it is a pharmaceutical, per the definition"*

Table 11: Table of challenges associated with preclinical safety data.

5.3.4 Clinical

Firm C was the only firm of the three cases who made it into the clinical trial phase of development, with a total of 21 clinical trials that have been sponsored by the firm. Firm C considers phase 3 clinical trials to be a significant challenge due to the level of capital required for the trials and the risk that clinically meaningful endpoints may not be reached.

> *"We don't want to do a phase 3 clinical trial, take it to the FDA and have them say, great, now you know, if you had looked at A, B and C – go back and do another study" – Firm C*

The task of obtaining clinically meaningful data from phase 3 clinical trials was a major regulatory challenge was also stated by Firm B. Firm B highlighted that the biggest hurdle that the firm can forecast will be the rigour of its botanical drug candidate in displaying to the FDA that it does generate clinically a meaningful outcome on its patient population.

> *"I think the single hurdle that stands out the most is if it works, you want to see the difference in a clinical trial" – Firm B*

5.3.5 Regulator ambiguity

Lack of regulatory clarity was reported as a barrier by all cases during botanical drug development. All firms reported that there were large levels of ambiguity from either the FDA's BDDGI document or from direct communication with the FDA. Firm A and Firm B stated that the guidance provided by the FDA through the BDDGI document was lacking in clarity in areas, specifically around preclinical development, manufacturing and standardisation controls. Firm B and Firm C also highlighted their frustrations with the lack of clarity in the direct communication with the FDA.

Firm A described its ordeal of stepping into the recently established botanical drug pathway as an experience of working in an area that was "*not very well defined*". The ambiguity of the FDA's BDDGI document led Firm A to follow a development route closer to that of a single molecule drug, to avoid any regulatory mishaps caused by ill-defined guidelines. Furthermore, Firm A relied entirely on a US consulting firm for all direct interactions with the FDA, to mitigate any further ambiguity.

> *"We know that getting things through, especially with lack of clarity, can become very expensive." – Firm A*

Firm B noted that the BDDGI released by the FDA for botanical drug development is broadly written and vague. Despite going through the established guidelines, Firm B still felt as if it may be at risk of rejection of preclinical data by the FDA, despite the encouragement it had received from its strategic and experienced partners. Furthermore, Firm B were frustrated with the FDA's lack of guiding communication despite Firm B being in direct communication with the FDA.

> *"So you're able to book an appointment with the FDA, but they're not allowed to make claims or clear direction where I say okay I've done this, would this be sufficient? They can say yes or no but can't go into any details so it's not really helpful. Especially if you embark, and then you spend a lot of money doing it." – Firm B*

5.3.6 Regulatory funding

The financial expenditure associated with the regulatory development of each case's botanical drug candidate was a challenge highlighted by all cases. Firm A, Firm B and Firm C all described the costs

associated with regulatory development to be high, however it was uniformly agreed that these costs are necessary in drug development to reach the market.

Firm B and Firm C both commented on the costs required for all the different components of regulatory drug development, and the inherent risks associated with large cash expenditures (refer to Table 12). While Firm A specifically mentioned capital resources as the largest regulatory challenge it faced. Firm A's ex-CEO recognised the lack of capital in of itself is not a regulatory-specific challenge, however, the sourcing of capital to enable development was the biggest challenge faced by the firm during development of its botanical drug candidate.

Case	Regulatory funding
Firm A	*"I think probably the biggest hurdle in botanical development was the structure of the company and capital. We had a clear way forward, but we got really bogged down and was pretty expensive."*
Firm B	*"Spin outs from a larger company with resources might sink a million dollars just into regulatory understanding. But we haven't got the resources or bandwidth to do so."*
Firm C	*"In the end, the FDA requires clinical trials for safety and those cost a lot of money, sometimes $20 million for a trial. Enough to put someone [a firm] under if they failed. That's why we need resources along the way to invest in those things."*

Table 12: Table of challenges associated with regulatory funding.

5.4 Firm strategy

The purpose of this section is to build a greater understanding of the strategies implemented and risk mitigation techniques used during the development of each case's botanical drug candidate.

5.4.1 Market choice

Firm A and Firm B decided to pursue the US market over their own local markets for strategic reasons to do with market size, patient population, regulatory accreditation and capital resourcing. Firm C chose the US market due to the patient population and as it is a US based firm. This is further elaborated in Table 13.

Case	Reasons for US market choice
Firm A	*"We had the pathway reasonably defined, but with the release of the guidelines, it opened the way. Plus we knew what the drug sales were in the US for migraines."*
Firm B	*"All other regulatory markets have jurisdiction or language barriers and the US is arguably one of the biggest pharma markets in the world"*
Firm C	"*Largest patient population of people suffering of antiretroviral induced diarrhoea"*

Table 13: Table of cases and why they chose the US market.

Firm B discussed how the FDA offered access to a large population under a blanket approval in the US. In contrast, other Western regulatory agencies such as the European Medicines Agency, do not grant access to all jurisdictions within Europe. Therefore, requiring additional regulatory work in each country to reach market in Europe. Firm B highlighted that by targeting the US market first, there would be a faster route to a market that is not impeded by language and country-specific regulations. Firm B also highlighted the significant intellectual property benefit offered by the US FDA botanical drug pathway, where generic drugs cannot be developed by competitors. Thus, protecting the value of the botanical drug once on market in the US.

5.4.2 Collaboration

The engagement in, and formation of strategic collaborative partnerships was a recurring theme identified across all cases. Collaboration and knowledge sharing through various parties was identified to help botanical drug development strategy. These different collaborative parties are represented in Figure 10.

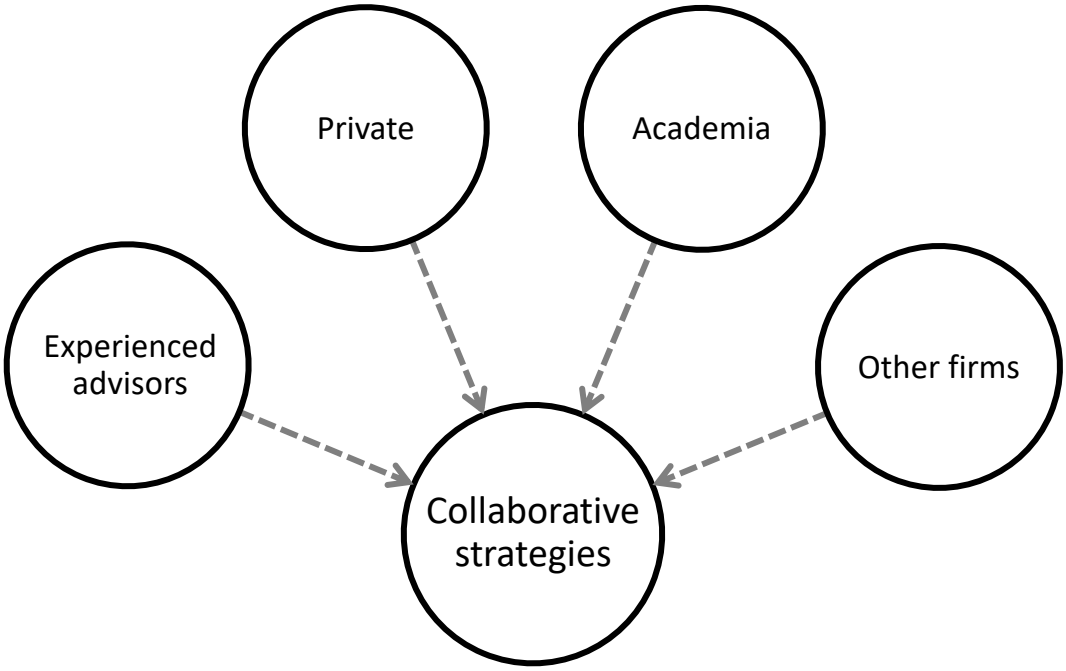

Figure 10: Identified collaborative strategies used by firms during botanical drug development.

All firms reported that collaboration with advisors with prior experience was valuable as the advisors' familiarity with both drug development and the regulatory process increased firm competence when developing strategies for botanical drug development. Knowledge sharing through collaboration with experienced advisors was central to Firm A and Firm B's regulatory and development strategies, as both the CEOs of each of the firms reported no prior experience in drug development.

Collaborative partnerships with private entities and individuals was a strategy highlighted across all cases. Firm A and Firm B both hired experienced US consultancy firms to facilitate development of their botanical drug products. Both firms described their partnerships with the US based consultancies as a central component of their development strategy.

> *"We actually contracted with them and they were really the guidance for all our documentation and everything to do with the FDA, so we relied on their capabilities" – Firm A*

Firm C discussed how it leveraged its specific scientific needs during early pre-clinical development. Firms and individuals with specialised assets and knowledge were contracted to help with the standardisation and identification of its botanical drug. Furthermore, Firm C engaged in a horizontal

asset integration strategy with two different FDA approved contract manufacturing organisations to produce its approved botanical drug API compound from the botanical raw materials.

> *"We collect the entire tree and the raw materials are then put into 55 gallon drums before being shipped to either India or Italy where the purification and extraction takes place. Then the pure API is shipped back to the US to be made into pills and sold." – Firm C*

Early collaboration with other firms and academia were both vital interactions in the formation of development strategies by all cases. Firm C described a pivotal part of its indigenous community supporting strategy was formed during conversations with other firms who have engaged in providing benefits back to local indigenous communities. While Firm A and Firm B both acknowledge the importance of collaborating with other firms who have experience with the FDA botanical drug development route. Furthermore, Firm A and Firm B both utilised academic collaborations in the discovery of their botanical drug candidates, while Firm C has leveraged academia for the expansion of their indications (refer to Table 14).

Case	Academic collaboration
Firm A	*"Our chair was the head of research over at Griffith, so I was there on campus with a private office. I got a lot of help from the Australian universities, from early contracted research through to presentations and exposure with raising capital "*
Firm B	*"I could have never done this alone. I literally went over it for years and years. I went to different professors at different universities with my idea, and said okay I've got this idea, come shoot it down, like tear it to shreds.* *It was very insightful to get their perspective"*
Firm C	*"Working with universities and research institutes is helping us understand how we can expand our indications"*

Table 14: Table of quotes on academic collaboration during botanical drug development.

5.4.3 Development strategy

All cases began development of their botanical drug candidate with a single goal target indication. However, all cases shared the same ultimate goal of indication expansion leveraging on the same end product through further clinical trials once on market (as shown in Figure 11). Target indications were also strategically chosen based on the market opportunity and the likelihood of development success by each case.

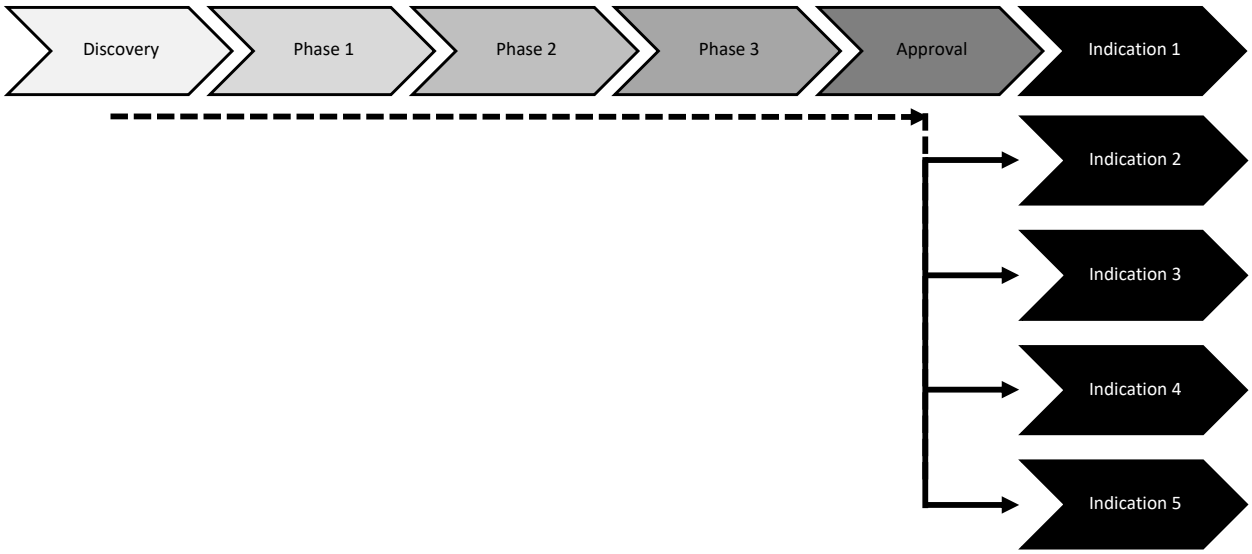

Figure 11: Figure of indication expansion of a botanical drug once approved for market.

Firm A and Firm C strategized to follow more of a traditional route of drug development, in a linear fashion through discovery to market approval before expansion of indications. Both firms felt that this was the best path to take due to the risk of relying on the unquantified previous human use claims. In contrast, Firm B had strategized to follow the botanical drug pathway outlined in the BDDGI for the development of its candidate. Firm B aims to leverage previous human use and conduct several its preclinical studies in parallel with phase 1- 3 clinical trials, followed by indication expansion once approved.

> *"I literally follow the guidance document. The chemistry, to toxicology and pharmacokinetics." – Firm B*

5.5 Risk mitigation

Risk mitigation is an important part of botanical drug development. All firms engaged in a number of risk mitigatory behaviours in an attempt to ensure that potential barriers during development are identified and managed.

Lack of previous experience with botanical drug development was a risk highlighted by all cases. As previously discussed, through knowledge sharing, collaboration and strategic partnerships, each firm attempted to reduce the risks associated with the lack of managerial previous experience. This is exemplified in Table 15.

Case	Risk mitigation
Firm A	*"Talking with others who have done direct development with the FDA and by bringing on our chairman, who is pretty experienced, helped make up for our inexperience."*
Firm B	*"But all the regulatory pathways will require consultants and we are going to need to keep minimizing that risk by getting experienced people to advise us as we go forward"*
Firm C	*"It's all about the risk mitigation through collaborative discussions and understanding what they [FDA] want to see."*

Table 15: Table of cases and how they mitigated the risk of inexperienced managers.

All cases mitigated developmental risks by engaging with the FDA directly or through a consultancy, to ensure that both the sponsor and the regulator were in agreement prior to investing in capital intensive trials. Firm A and Firm B both stated the importance of having multiple parties audit decisions before they are made to mitigate potential risks and confirm that all information presented to the FDA is satisfactory. Furthermore, Firm A and Firm B stressed the importance of cross-checking proposed actions before final decisions were made and the actions implemented, to ensure that the FDA did not require amendments, which would result in additional expenses and time delays for the firm.

> *"I only recently learned is that one of the reasons we're prepping so much for our initial application is that if the FDA comes back with suggest amendments, the comments will be*

public. I know, pharmaceutical companies do tend to look at these and use them as one of the strategies to squash smaller companies. So we are trying to avoid that risk and stay under the radar."

Chapter 6: Discussion

This research was an exploratory study which aimed to do two things. First, identify the major regulatory challenges faced by firms during botanical drug development. Second, understand how these firms strategized to satisfy regulations set by the US FDA when attempting to gain market approval. This was achieved through the building of three firm-oriented case studies. Each case represented a firm which had a botanical drug candidate with a different regulatory outcome; failed, ongoing or approved. The different regulatory outcomes meant that the learnings from each case may offer insights on the same subject matter, but from different angles (Stavros & Westberg, 2009). These cases were built using in-depth semi-structured interviews and a range of secondary data sources.

Across multiple case data, there were a number of shared regulatory challenges identified including: chemistry and control challenges; manufacturing challenges; preclinical development challenges and clinical development challenges. All of which fell in-line with the botanical drug development challenges identified within the literature review. Furthermore, regulator ambiguity and regulatory funding were additional challenges identified from this research which were not heavily emphasized within the botanical drug development literature.

The strategies and risk mitigation techniques implemented by cases during botanical drug development were explored through the multiple case study design. The strategy and risk data obtained is intended to help generate a greater understanding of how firms engage in botanical drug development with a particular interest in the inter- and intra-case specific regulatory challenges identified relative to the firm's regulatory outcomes.

The purpose of this section is to interpret and describe the significance of the case study research findings on regulatory challenges, firm strategies and risk mitigation in light of what is already known and described within the literature. First the regulatory challenges and regulation characteristics described from the data will be discussed, followed by the identified firm strategies and how risk was mitigated.

6.1 Regulatory challenges

All case studies faced multiple regulatory challenges in the development of their botanical drug candidate. Upon analysis and comparison of the multiple case study data, it is apparent that during botanical drug development most challenges faced by the cases arose in the early stages of the development process, prior to the submission of the IND application. These challenges were found to occur within the *Chemistry, manufacturing and controls* and the *Preclinical data* legs of the Hoffman (2015) three-legged stool of the IND process as previous described in section 3.2.2 of the literature review (refer to Figure 8). Furthermore, these challenges were also found to be within the same areas identified and discussed within the literature. However, two additional challenges were identified from the data that were not discussed within the literature review. These additional challenges were associated with regulator ambiguity and costs involved in obtaining regulatory approval.

6.1.1 Chemistry, manufacturing and controls

Within the *Chemistry, manufacturing and controls* leg of Hoffman's (2015) IND stool, firms found challenges with the standardisation of their botanical drug candidate and in their manufacturing processes. The standardisation challenges consisted of a lack of controls for batch to batch consistency, adequate identification of all the mechanisms of action, stability controls and the complete characterisation of components within the botanical drug candidate. Furthermore, firms found that obtaining GACPs was a challenging process due to the scale, raw botanical material inconsistencies and ethical requirements set by the FDA.

Firm A may be considered as an outlier from all standardisation and GACPs challenges, apart from stability control. The extensive previous research and development conducted by Firm A's parent company on the use of the raw botanical materials in dietary supplements meant that all manufacturing and standardisation was established prior to the inception of the firm. Therefore, apart from the initial stability issues of including a secondary active to stabilise the botanical drug candidate, Firm A did not face any specific challenges with the *Chemistry, manufacturing and controls* leg of Hoffman's (2015) IND stool.

6.1.2 Preclinical data

Within the *Preclinical data* leg of Hoffman's (2015) IND stool, firms found challenges in the guidance offered by the FDA regarding what may be considered adequate safety data based on previous human use. The challenges associated with preclinical safety data in botanical drug development is discussed within the literature. Wu et al. (2000) investigated botanical drug IND applications and found that 26.24% of submitted applications required further regulatory guidance due to deficient preclinical information. This was not reflected in the outcomes of this research, as only one case had progressed through the IND application and did so without requests for further safety data. Regulator requests for additional information are strategic roadblocks for firms during early development as they extend development timeline and can place additional financial constraints on firms. While the FDA offers advice through its published BDDGI document on what evidence it expects for preclinical data, the case data gathered in this research suggests that this information is ambiguous to the point where it presents itself as a challenge to firms.

Of the three cases built in this research, two followed standard toxicology animal safety testing. Firm C stated that it followed this route as at the time the FDA had not yet announced the feasibility of leveraging previous human use as an alternative to traditional safety studies in botanical drug development. The second case, Firm A, encountered challenges and ambiguity with the leveraging of previous human use, and decided to mitigate any potential downstream issues by also conducting standard animal toxicology safety testing studies. The third case, Firm B, is currently leveraging previous human use as safety data. As highlighted by Dou et al. (2019), leveraging previous human use may provide a faster access to phase 1 and 2 clinical trials, but places firms at risk of additional downstream safety requirements from the FDA. Firm B understands and specifically mentioned that its data may be not deemed adequate for phase 3 trials. Firm B acknowledges the risk that the FDA may require further information to be obtained through traditional safety trials later in development. As highlighted by Wu et al. (2020) the FDA makes decisions on a case-by-case basis, however rigorous safety data is often a prerequisite for phase 3 trials to take place.

6.1.3 Clinical data

There were no challenges unique to botanical drug development found within the *Clinical data* leg of the Hoffman (2015) IND stool. However, challenges regarding regulator communication and clinical trial

designs were identified. Furthermore, the unknown risk of whether the botanical drug candidate is efficacious and the substantial capital requirements to fund phase 3 trials were expressed as concerns by all cases.

Firm C is the only case in this study that progressed through clinical development. Firm C found that communicating with the FDA for the planning of their indication expansion phase 3 clinical trials, was challenging and time consuming due to the ambiguity and constant back and forth between different teams at the FDA. The communication with the FDA regarding trial design was the only identified regulatory challenge during clinical development by Firm C.

Risks associated with proving drug efficacy and the funding of the trials themselves were concerns raised by all cases. These concerns are not new and are well identified within the literature as they are the standard risks associated with biotechnology and drug development industry as a whole (Ciociola et al., 2014). However, these concerns were not specifically challenges faced, but rather coming risks and known unknowns (Kaplan, 2009).

6.1.4 Regulator ambiguity

All cases highlighted challenges associated with regulatory communication from the FDA. Firm A and Firm B both expressed frustration with the ambiguous nature of the information presented within the FDA's BDDGI document. While Firm B and Firm C both expressed frustration with the lack of clarity from the FDA when in direct communication.

As previously stated, communication challenges were faced by Firm C in the development of clinical trial designs for the expansion of indications of the firm's approved botanical drug. Frustrations were expressed by Firm C in the ambiguity of communication between the firm and the regulator, which resulted in two years of discussions before phase 3 indication expansion trial designs were finalised. Firm B highlighted frustration associated with the lack of regulatory guidance when in direct communication with the FDA. Firm B felt that answers to its questions lacked depth and were responded to in a closed "yes / no" fashion.

As described in section 2.2.1, the FDA released the BDDGI as an attempt to address the challenges associated with developing botanical drugs and to encourage and facilitate botanical drug development (Wright, 2021). As highlighted by Hoffman (2005) and Dou et al. (2019), the complex polymolecular nature of botanical drugs means that no two drug candidates may be the same, and will therefore require case-specific scrutiny during development. The existence of a document offering botanical drug development guidance poses a challenge within itself, as the recommendations must be generic enough to match a range of different botanical drug candidates while simultaneously containing information on specifics. Firm B described the BDDGI as more of a "what the FDA wants to see" document, rather the preferred "how can we show this". Regulator clarity is essential for development as it enables timelines to be kept short and production costs to remain low (Plagnol et al., 2009). For this reason, Firm A used an experienced regulatory consultancy for all direct communication with the FDA.

The challenges associated with clarity of communication with the regulator are also reflected within the literature. Plagnol et al. (2009) found that multiple firms expressed uncertainty and lack of clarity in communication of regulatory expectations. Understanding the regulatory requirements processes and challenges is vital when charting a development path because this knowledge will impact the developmental strategies and testing decisions along the way (Shimasaki, 2009b)

6.1.5 Financing botanical drug development

Finance is a major part of any venture. Drug discovery and all the activities required for regulatory development are capital intensive and time consuming. Drug development can cost firms up to $2.6 billion US and take 12 years or more to progress from discovery to market (DiMasi et al., 2016). In early stages of development when capital resources are scarce, loss of finances due to inconclusive trials can mean the death of a firm (Mohs & Greig, 2017).

The purpose of this research was to identify not only the regulatory challenges but also the strategies used by firms in botanical drug development. As financing in life sciences is a complex topic of its own, it was not a focus for this research and was not included in the literature review or study design. However, all cases stated that financing the regulatory development of their botanical drug product was a major challenge. With Firm A ultimately failing to develop its botanical drug candidate due to the lack of capital available for further development. This study therefore illuminated a further field for future

study into how financial challenges affect strategic decision making when attempting to get a botanical drug to market.

Firm B and Firm C expressed their frustration with the cost of regulatory development. Regulatory development is a large and risky financial commitment for firms (Ciociola et al., 2014). In line with the literature, both Firm A and Firm C felt that the high costs place large risks on the financial stability of the firm. All cases shared the view that failure in obtaining meaningful data from trials is where the real funding risk exists, as it meant that trials would have to be repeated. Furthermore, Firm A stated that acquiring funding was the biggest hurdle the firm faced during their entire development experience, ultimately resulting in the failure of the firm. Based on the data, the cost of capital is a major risk factor to firms developing botanical drug candidates which needs to be adequately managed if firms hope to see success of their botanical drug candidate.

6.2 Regulation

Understanding the regulator-firm relationship is important in strategy formation and risk mitigation, as it allows both parties to understand what is expected (Rose & Ceres, 2017).
The case study data uncovered shared challenges regarding a lack of clarity with regulatory communication and ambiguity within the BDDGI guidance document. The conclusion from the data suggests that the FDA's communication with firms who are undergoing botanical drug development is suboptimal, presenting itself as a notable challenge.

It is important that effective communication between regulators and firms is achieved as ideally the two should working in a collaborative manner during the drug development process with a shared public health goal of making safe, effective and high-quality drugs available to patients (Rose & Ceres, 2017). Furthermore, the communication challenges faced by firms may be attributed to the regulatory approach undertaken by the FDA. The existence of the BDDGI document offering generic guidance to firms, can be considered evidence that the FDA follows a system based regulatory approach. The system based regulatory approach revolves around the notion that the regulator wants to promote firms to self-regulate to ensure synergy between firm processes and compliance expectations (de Bree & Stoopendaal, 2020). de Bree and Stoopendaal (2020) argue that through the lens of the system based regulatory approach, the BDDGI document acts as a synergy promoting resource as it decreases the

level of compliance enforcement needed by FDA during development. de Bree and Stoopendaal (2020) claim the BDDGI does so by offering guidance and promoting firms to undertake self-regulation to increase internal quality standards.

In practice, all cases found the BDDGI document to be both insightful yet ambiguous in its guidance and expectations. As previously stated, the insightfulness may stem from the general approaches and expectations on what data the regulator needs, which promotes self-regulation within firms. Furthermore, the ambiguity may be due to the cases looking for "how" answers from a guidance document which was developed for generalisation of a broad development pathway.

6.3 Firm management

The strategic approaches in biotechnology firms are not different to those in other industries, which are moulded by both internal and external factors (Molloy & Johnson, 2016). The purpose of understanding the strategies and risk mitigation techniques used by firms is to uncover how they may have helped to increase the possibility of firm success and survival, or identify areas where firms underperformed leading to negative outcomes (R. S. Kaplan, 2009; Wong, 2011).

The firms in each of the three cases were founded by individuals with no prior experience in botanical or small molecule drug development, and all chose the US market as their primary market goal. The study data reflected that the US was strategically chosen for a number of external factors including patient population access, market size, regulatory accreditation and the increased ability of firm access to capital in the US. Internal factors influencing market decision consisted of the recognition of gaining FDA approval and existing supply chains and products on market as dietary supplements. Furthermore, the FDA offers competitor protection as generic botanical drug products cannot be developed for market. Unlike small molecule drugs, individual botanical drugs candidates are approved, rather than the API or molecule itself (Wu et al., 2020).

6.3.1 Firm Strategies

There were differences in the long-term strategic goals of each case. Firm A and Firm B both aimed to completely develop and market their botanical drug candidates themselves through vertical integration, building manufacturing and distribution capabilities. Both cases then planned on expansion of their

indications and growth into other regulatory markets such as Europe and Asia. Firm A and Firm B were both following a "novel compound type" development strategy highlighted by Pisano (2006). Both cases planned to reduce the risk of operating in an inefficient market for know-how, caused by the unique tacitness of each botanical drug candidate, by aiming to vertically integrate with their downstream assets. However, this development strategy inadvertently puts firms at higher risk due to increased regulatory and capital requirements (Gans & Stern, 2003; Pisano, 2006).

Firm C planned to exit after proof of concept in early clinical development via licensing to a more clinically capable firm. Firm C initially identified as a ethnobotanical drug discovery firm, and stated that it was not interested in conducting clinical drug development itself. Since regaining rights to their botanical drug candidate, Firm C has horizontally integrated at all levels of the value chain and leveraged contract research and manufacturing facilities for further development and manufacturing of their botanical drug. Interestingly, Pisano (2006) states that firms who horizontally integrate with an innovation that fits the "novel compound type" category often operate in an ineffective market for knowledge and historically have high accounts of legal disputes. Pisano's (2006) recommendation against horizontal integration in the "novel compound type" category because of the prevalence of legal disputes was borne out in this study. Firm C had filed a lawsuit against their botanical drug's licensee and developer, due to alleged breaches of the botanical drug development agreement.

Pisano (2006) argues that for biotechnology firms to perform well they must leverage partnerships across different disciplines and parties. There is no clear pathway on how to achieve an effective strategy within the biotechnology industry as each firm is unique, especially within botanical drug development (Shimasaki, 2009b). All cases engaged in collaborative partnerships with multiple stakeholders at different stages of development. Collaborative partnerships were formed with academia, private researchers and consultancies, other firms developing botanical drugs and experienced individuals. These collaborations and alliances were strategically formed to share complementary assets between parties to increase the knowledge base of each firm, reduce risks and thus increase the likelihood of success through better informed decisions (Pisano, 2006). Furthermore, Case C strategically formed collaborative relationships with local communities where the raw botanical materials were sourced. Following Firm C's founding principles, this strategy built local infrastructure and returned economic benefits to the communities where the traditional use of the botanical raw material originated, while simultaneously meeting the GACPs expectations set by the FDA.

All cases strategized to get their botanical drug candidate to market as fast and as effectively as possible. Two key strategies, indication optimisation and parallel clinical trials were identified from the study data as means to achieve this.

All cases aimed to expand on their botanical drug candidate's indications once regulatory approval had been achieved. From the study data obtained, complex polymolecular botanical drugs can often have multiple possible target indications. As mentioned within the literature, firms with multi-indication therapeutics may be attracted to developing their product for indications in populations that have a higher probability of success, high market attractiveness, and are eligible for streamlined regulatory pathways such as orphan status or accelerated approval (Nielsch et al., 2007). Using value driven drug development strategies targeting specific indications or populations, botanical drug firms can leverage the most efficient route to market, achieving revenue faster (Nielsch et al., 2007). This can then be followed by further expansion of indications as Firm C is currently doing.

Firm A and Firm C both followed a traditional linear drug development strategy as highlighted by Hughes et al. (2011) in Figure 1. This is due to both cases opting to develop their botanical drug candidates through more traditional small molecule drug pathways, as previously described. While Firm B is currently undertaking a parallel trial strategy in the development of their botanical drug candidate.

Firms can use parallel clinical trial strategy to leverage the alternate development pathway offered by the FDA for botanical drug candidates. Where preclinical and clinical trials can be conducted at the same time in parallel on the basis that there is satisfactory previous human use data available (Wu et al., 2020). This strategy enables faster development of botanical drugs at a higher risk, as all required trials do not have to be undertaken in series. Discoveries which would traditionally be found in a range of preclinical studies (refer to Table 6) prior to clinical trials, would be found during clinical trials in firms undertaking parallel strategies. This may result in necessary repetition of late-stage trials to include this new information, especially if it is related to chronic conditions such as cancer (Milani & Pathak, 2018).

The study data collected in this research suggests that all cases had intended strategies from the outset of development of their botanical drug candidate. However due to the multifaceted complexities of drug development and the biotechnology space, firms were unable to follow generic stage-oriented

strategies such as the strategic planning process (Figure 2) highlighted by Muller (2002). All cases unintentionally followed the real-world strategy concept coined by Mintzberg (1978), where multiple interactions from different stakeholders converged causing emergent strategies to form. Thus, altering the realised firm strategies from that originally intended (Mintzberg, 1978). The key finding was that firms must be fluid and decisive to allow new strategies to form as new information is presented and the needs and challenges of the regulatory development process changes.

6.3.2 Risk mitigation

The collaborative partnerships and indication expansion strategies identified within the case study data, exhibits risk mitigation as a by-product of the strategy used. Specific risk mitigation behaviours were also identified across the case study sample data. Risk mitigation is about identifying and overcoming obstacles that a strategy may encounter along the way (Kaplan, 2009). Mitigating risk does not advance firm strategy but does alleviate barriers that would otherwise slow firms from reaching the desired strategic outcome (Kaplan, 2009).

The case data shows that all firms engaged in risk mitigation during development of their botanical drug candidate. All cases were founded or managed by managers who had no prior experience in drug development and were conscious of their lack of expertise within the area. Kaplan (2009) found that managers and senior executives failed to spend sufficient time engaging in risk management and strategy. However, this was not reflected in the data of this study. In fact, managers from Firm A and Firm B developed a method for decision making, where all decisions were audited through different collaborative partners to ensure adequate strategy risk mitigation was continuously being conducted where necessary. While Firm C completely mitigated the risks associated with clinical drug development by out licensing all of the clinical research which initially led to the approval of their botanical drug.

The most common risk mitigation technique identified from the study data, was to engage in collaborative partnerships. As previously stated, consultancy and advisory partnerships with experienced individuals and firms were established to build knowledge base and increase the possibility of firm success. Risk associated with regulation expectations was also minimised through communication with the FDA by all cases. Firm A and Firm B strategically did this with the help of regulatory consultancies to mitigate any communication ambiguities between the regulator and

regulated. While Firm C spent two years communicating, de-risking and planning two phase 3 indication expansion trials for their approved botanical drug.

No cases mentioned the use of any specific risk mitigatory tools such as real options reasoning approach or the stage gate method (Cooper, 2008; McGrath & Nerkar, 2004). Risk was managed mainly though leveraging previous experience and communication with different stakeholders. Simple risk mitigation tools such as forecasting, brainstorming and uncertainty exploration can be the difference between life and death of a firm, especially within the high-risk biotechnology industry (Ekanayake & Subramaniam, 2012; Wong, 2011). These tools offer benefits to firms, especially firms earlier in their development lifecycle. (Ekanayake & Subramaniam, 2012).

As found by Vanderbyl & Kobelak (2008), firms who have a comprehensive risk management system integrated within their strategy, often have a competitive edge when it comes to attracting capital and investors. Unfortunately, Firm A failed to recognise the major strategic risk of having a significant shareholder as a nutraceutical company. This was an unknown strategic risk, as when Firm A attempted to raise further capital it found that investors were unwilling to invest in a drug development firm that had a nutraceutical company holding equity, and sitting on the board. Ultimately the lack of interest from investors caused the firm to fail development of its botanical drug candidate and succumb to a lack of capital.

What happened to Firm A highlights the importance of including a risk mitigation tool alongside the firm strategy. Firm A may have benefited from implementing a real options reasoning approach due to the high uncertainty and financial risk around the feasibility of their botanical drug candidate. Real option reasoning is also recommended for Firm C. While Firm B would have benefited from a stage gate method.

Using real options reasoning as a risk mitigation tool would have been appropriate based on the linear traditional small molecule drug development strategy Firm A was following. Furthermore, the real options reasoning consists of multiple stages, with three distinct phases at each stage (opportunity, analysis and option as highlighted in section 3.1.2.1). The second and third phase of real options reasoning may have alerted Firm A's management of the looming strategic risk of having a nutraceutical company on the board, and as a major shareholder, of a pharmaceutical drug development firm.

Firm C would benefit from real options reasoning while conducting indication expansion studies, due to the requirement of large sums of investment prior to each phase 3 trial. This approach allows risk to be managed by both the firm and the investor through mapping of possible resource pathways which can aid in the facilitation of decision making (Miller & Waller, 2003).

The stage gate method would have facilitated better analysis of each major decision made by Firm B. Firm B strategized to undertake a development pathway leveraging previous human use without sufficient evaluation as to whether this pathway may impose temporal, financial and safety risks to the firm in the future. Using the stage gate method could have promoted a mechanism enabling Firm B to partake in further development and market risk analysis. An example could be increasing communication with the FDA to discuss data on previous human use and coming to an agreement of what is needed to satisfy the regulator's expectations. Therefore, if the available previous human use data fails to meet a benchmarked criteria indicating risk, then Firm B could pivot and follow a linear development pathway like that which was strategized by Firm A and Firm C.

6.4 Strengths and limitations

6.4.1 Limitations

This research contributes to the majorly unexplored topic of the challenges and strategies associated with botanical drug development. However, as with all research there are limitations which may have put constraints on the outcomes of the data. It is key that limitations are pinpointed so that actions can be taken to reduce the risks they impose on the legitimacy of the data. Several limitations including time, sample size, sample selection and interview considerations were identified.

Time constraints generated several limitations in this research. Due to a late pivot in research topic, there were constraints on the case sample sizes and data collection capabilities. A total of 21 firms were contacted for inclusion in this research, with only three responding and being included within the data. The small sample size limits the insights and generalisability which may have been available from a larger sample. Furthermore, the low response rate leading to the small sample size may be due to the short time period between firms being contacted and the beginning of data analysis.

There are limitations in the generalisability of representation of the research findings. This is due to the non-random purposive selection of case study participants which occurred through company benchmarking and snowball sampling. However, fortunately generalisation of outcomes was not the purpose of this case study research. The aim was to gain an increased understanding of the unique challenges and strategies specific to each firm during botanical drug development, where relative findings could be leveraged by other firms who look to follow this development pathway.

Limitations associated with the obtained data were also identified. Informants relied on retrospective recall of consideration factors, strategies, and risk mitigation techniques or they discussed prospective plans that have not yet been implemented. This meant data provided during in-depth interviews may have been subjected to recall bias or failure of accurate prediction of future factors and processes. However, through convergence of evidence via triangulation of primary and secondary data sources, and inclusion of multiple case studies are different stages of botanical drug development, these data limitations were mitigated.

Another limitation was the use of multiple podcast in-depth interviews. One of the research cases used multiple podcasts as a data source where primary in-depth interviews were unavailable. The podcasts were a limitation as the informants in the podcast were not answering questions formed specifically for this research. However, the inclusion of these podcasts did in-deed give further depth to the otherwise available data, particularly due to the time constraints this study faced and therefore the limitations of including this data is outweighed by the multi-dimensionality this data provided to the study data. All podcasts were on the theme of the research topic, discussing firm strategy and challenges during botanical drug development. Additionally, the data from these podcasts were coded for relevant themes before triangulation with other secondary sources to build a case.

6.4.2 Strengths

Although several limitations placed constraints on the legitimacy of the research, there were a number of strengths which also improved the construct validity and quality of the research.

A strength of this research was the specificity and focus on a small sample at different stages of botanical drug development, which provided a high level of context and understanding of the challenges

faced and management strategies implemented by firms. Furthermore, multiple cases at different stages of development were able to provide unique insights on successful and catastrophic challenges and strategies that were unique to each case based on their development progress.

The maintenance of a company benchmarking and case study database enabled a chain of evidence to be formed, improving the reliability and dependability of the research findings. While the use of multiple case studies constructed from a number of different data sources enabled the triangulation of intra- and inter-case research findings. Thus, providing a high level of transferability to the results.

Another strength was the methodological approach taken in this research. An inductive exploratory approach allowed for the identification of challenges and strategies in the unique context of this research without the bias from any preconceived hypotheses. This facilitated the observed results to contain minimal influence from the researcher and closely reflect that of the real world.

Chapter 7: Conclusion and recommendations

The purpose of this section is to conclude the research findings and provide recommendations for future botanical drug development firms based on these findings. Implications for both industry and academia are also provided based on the research outcomes described.

7.1 Conclusion

Using a multiple case study, exploratory qualitative research approach, this thesis explored the question:

> *What are the major regulatory challenges faced by firms during botanical drug development, and how do firms strategize to satisfy regulations when attempting to gain US FDA market approval?*

This question was broken down into three sub-questions which were then addressed through the building of multiple case studies:

1. *What are the major regulatory challenges in botanical drug development?*
2. *How do firms strategize to satisfy the FDA regulatory requirements, and specifically, how do the major regulatory challenges identified in this thesis influence or alter how firms strategize during botanical drug development?*
3. *How do firms minimise risk during botanical drug development, and specifically, how do firms minimise risk associated with these major challenges?*

Through analysis of the case study data and the assessment of the academic literature, multiple shared regulatory challenges associated with botanical drug development were identified. Furthermore, strategies and risk management techniques used by firms during the development of botanical drugs were found.

i. Chemistry, manufacturing and controls contained the largest number of regulatory challenges faced by firms developing botanical drug candidates for the US market. These challenges consisted of batch to batch consistency controls, identification of mechanisms of action, stability

controls and characterisation of botanical drug candidates. Manufacturing challenges were oriented around plant cultivation. Firms found difficulty in controlling contaminants and inconsistencies in botanical raw material at scale, and setting up GACPs.

ii. Leveraging previous human use as safety data was a regulatory challenge due to a lack of clarity on whether additional information may be required to facilitate late stages of clinical development. This places firms at risk of downstream financial costs which threatened the validity of previously completed studies.

iii. Communication of regulatory expectations from the FDA was a challenge faced by botanical drug development firms. Direct communication lacked clarity and guidance documents such as the BDDGI were ambiguous.

iv. Botanical drug development firms found challenges in the financing of regulatory botanical drug development. The high cost of capital associated with all regulatory development activities places large risks on firms. However all cases agreed that these costs are a necessary part of drug development.

v. Management structure of botanical drug development firms is critical for attracting capital for further regulatory development.

vi. Strategic collaboration with multiple stakeholders throughout botanical drug development increases firm knowledge base and decision making skills, increasing the likelihood of a successful strategy.

vii. Botanical drugs can be multi-indication products and firms focus on a strategic indication which offers a safer, faster route to market before expanding indications into other areas.

viii. Botanical drug firms engaged in different development strategies such as parallel clinical trials or linear drug development strategies. Furthermore firms attempt to integrate with the industry through both vertical and horizontal means. No indication on the most optimal development and integration strategies can be extrapolated from this research.

ix. Firms were found to mitigate risk mainly through collaborative partnerships. External collaborative partnerships with consultancies were used to mitigate communication risks with the FDA. Internal collaborative partnerships with strategically onboarded experienced individuals were used to audit decisions. No risk mitigation tools were found to be used by firms during botanical drug development.

7.3 Recommendations

The following recommendations have been derived from the findings of the research. These recommendations aim to provide considerations which can help botanical drug development firms mitigate risk and strategize to overcome regulatory challenges.

i. Early engagement in collaborative partnerships is vital for building a knowledge base. Firms who are engaging in botanical drug development should seek to onboard partners early in the development process. These partners should have prior experience with a same or similar background to the industry, so that their input can increase the likelihood of the implementation of effective strategies (Shimasaki, 2009a).
ii. Early engagement in communication with regulators is vital to maximise harmonisation of expected development outcomes (Rose & Ceres, 2017). Early engagement with the FDA can contribute to construction of regulatory strategies through feedback and clarification of regulations. Firms should engage in external consultancies to streamline communication with the FDA to ensure both the regulator and firm are in harmonisation and understand one-another's needs (Shimasaki, 2009b).
iii. Since the botanical drug development challenges appear to be the greatest at the start of the drug development process, and these challenges are located within the preclinical, chemistry, manufacturing, and controls stages of the drug development process, two recommendations have been formed to help mitigate these challenges. First, firms should engage with regulatory consultants who have polymolecular drug development experience, to streamline all chemistry, manufacturing, and controls challenges. Second, firms should conduct traditional safety trials and follow a linear drug development strategy, mitigating the downstream risks associated with leveraging previous human use.
iv. Risk mitigation tools should be implemented to help predict and mitigate any future hurdles in firm drug development strategies. Using risk mitigation tools, firms can increase understanding and prepare for known, known unknown, and unknown unknown risks. Thus, increasing the probability of development and firm success.
v. It is important that there is a uniform stakeholder consensus on the long-term goals of the firm. Furthermore, firms need to understand the needs of their future investors and should

strategically build the structure of their firm to generate interest from these parties in the future to avoid hitting capital walls.

7. 4 Industry implications

As demonstrated above, the data generated from this multi-case study research has formed a list of key recommendations that may be useful to firms who wish to develop and commercialise a botanical drug for the US market. The findings from this research may be used to inform these firms about the different regulatory challenges they may face and provide insight in how to mitigate these challenges in the future.

Firms planning to develop their own botanical drugs should analyse the strategies used by firms in this research, so that they may use these learning to mould and modify their own. Furthermore, it is hoped that risk mitigation techniques used in the case data and the recommended risk mitigation tools included in the discussion are implemented by these firms when traversing the botanical drug development pathway.

This research has also identified the importance of firm structure regarding capital and investment. It is hoped that future firms structure their board and organisation to fit the needs and interests of future investors to avoid hitting a capital wall.

7. 5 Academic implications

This research undertook an exploratory qualitative approach to understand the regulatory challenges, firm strategy and risk mitigation techniques of firms developing botanical drugs for the US market. This research contributes to the existing literature in two ways:

i. This research contributes by identifying and confirming the current regulatory challenges associated with botanical drug development in the US. Currently, literature on these regulatory challenges exists, although it is limited, and this research provides an up-to-date perspective.
ii. This research contributes greatly to the strategic and risk mitigation management literature in context of US botanical drug development, as currently there are no prior studies that exist in this area.

7.6 Future Research

Future research should audit the effectiveness of firm management in botanical drug development. This research was concerned about how firms strategize, while future research should analyse the most effective firm strategies and risk mitigation techniques used during botanical drug development. Furthermore, a larger sample size may increase the generalisability of data which could facilitate creation of industry guidelines on best botanical drug development practices in development for the US market. Sample size may be increased through two methods. First, future researchers can attempt to leverage industry partners to facilitate introductions with botanical drug development firms so that a larger sample size may be obtained. Second, removing time constraints may increase sample size due to inclusion of firms who may respond to study invitations late.

This study also illuminated an area of future research through the analysis of the case study data. Each case demonstrated that firm capital had a clear impact on botanical drug development and the strategic decision making of firms. While this was not a focus for this study, its prevalence of appearance throughout the cases suggest it is an area where future research should continue.

References

Abraham, J. (2003). Learning from drug disasters and reforming medicines regulation. *Critical Public Health*, *13*(3), 269–279. https://doi.org/10.1080/0958159032000114462

Adner, R., & Levinthal, D. A. (2004). What Is Not A Real Option: Considering Boundaries for the Application of Real Options to Business Strategy. *Https://Doi.Org/10.5465/Amr.2004.11851715*, *29*(1), 74–85. https://doi.org/10.5465/AMR.2004.11851715

Ahn, K. (2017). The worldwide trend of using botanical drugs and strategies for developing global drugs. *BMB Reports*, *50*(3), 111–116. https://doi.org/10.5483/BMBREP.2017.50.3.221

Alotiby, A. (2021). The Impact of Media on Public Health Awareness Concerning the Use of Natural Remedies Against the COVID-19 Outbreak in Saudi Arabia. *International Journal of General Medicine*, *14*, 3145. https://doi.org/10.2147/IJGM.S317348

Altamuro, J. L. M., Gray, J. v., & Zhang, H. (2022). Corporate Integrity Culture and Compliance: A Study of the Pharmaceutical Industry*. *Contemporary Accounting Research*, *39*(1), 428–458. https://doi.org/10.1111/1911-3846.12727

Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., Orhan, I. E., Banach, M., Rollinger, J. M., Barreca, D., Weckwerth, W., Bauer, R., Bayer, E. A., Majeed, M., Bishayee, A., Bochkov, V., Bonn, G. K., Braidy, N., Bucar, F., Cifuentes, A., D'Onofrio, G., Bodkin, M., … Supuran, C. T. (2021). Natural products in drug discovery: advances and opportunities. In *Nature Reviews Drug Discovery* (Vol. 20, Issue 3, pp. 200–216). Nature Research. https://doi.org/10.1038/s41573-020-00114-z

Ayres, I., & Braithwaite, J. (1992). *Responsive Regulation: Transcending the Deregulation Debate*. Oxford University Press, USA.

Beaussier, A. L., Demeritt, D., Griffiths, A., & Rothstein, H. (2016). Accounting for failure: risk-based regulation and the problems of ensuring healthcare quality in the NHS. *Http://Dx.Doi.Org/10.1080/13698575.2016.1192585*, *18*(3–4), 205–224. https://doi.org/10.1080/13698575.2016.1192585

Benfield, J. A., & Szlemko, W. J. (2006). Internet-based data collection: Promises and realities. *Canada Journal of Research Practice Journal of Research Practice*, *2*(2).

Best, S., & Krueger, B. (2004). Internet Data Collection. In *Internet Data Collection*. SAGE Publications, Inc. https://doi.org/10.4135/9781412984553

Bilia, A. R., & Costa, M. do C. (2021). Medicinal plants and their preparations in the European market: Why has the harmonization failed? The cases of St. John's wort, valerian, ginkgo, ginseng, and green tea. In *Phytomedicine* (Vol. 81). Elsevier GmbH. https://doi.org/10.1016/j.phymed.2020.153421

Bode-Greuel, K. M., & Nickisch, K. J. (2008). Value-driven project and portfolio management in the pharmaceutical industry: Drug discovery versus drug development - Commonalities and differences in portfolio management practice. *Journal of Commercial Biotechnology*, *14*(4), 307–325. https://doi.org/10.1057/JCB.2008.6

Braithwaite, J. (2006). Responsive regulation and developing economies. *World Development*, *34*(5), 884–898. https://doi.org/10.1016/J.WORLDDEV.2005.04.021

Brown, S. L., & Eisenhardt, K. M. (1995). PRODUCT DEVELOPMENT: PAST RESEARCH, PRESENT FINDINGS, AND FUTURE DIRECTIONS. *Academy of Management Review*, *20*(2), 343–378.

Burns, L., Housman, M., & Robinson, C. (2009). Market Entry and Exit by Biotech and Device Companies Funded by Venture Capital. *Health Affairs*, *28*(1), 76–86. https://doi.org/10.1377/hlthaff.28.1.w76

Carter, N., Bryant-Lukosius, D., Dicenso, A., Blythe, J., & Neville, A. J. (2014). The use of triangulation in qualitative research. In *Oncology Nursing Forum* (Vol. 41, Issue 5, pp. 545–547). Oncology Nursing Society. https://doi.org/10.1188/14.ONF.545-547

CFR - Code of Federal Regulations Title 21, Pub. L. No. 21CFR312 (2021). https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.2

Checo, G., Lokhande, J. N., & Lokhande, S. (2019). Regulatory Perspectives of Botanical Drug Products in Top Pharmaceutical Markets. In *Botanical Drug Products: Recent Market Trends* (1st ed., pp. 19–38). CRC Press, 2019. http://ebookcentral.proquest.com/lib/auckland/detail.action?docID=5601901.

Chen, C. H., Dickman, K. G., Moriya, M., Zavadil, J., Sidorenko, V. S., Edwards, K. L., Gnatenko, D. v., Wu, L., Turesky, R. J., Wu, X. R., Pu, Y. S., & Grollman, A. P. (2012). Aristolochic acid-associated

urothelial cancer in Taiwan. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(21), 8241–8246. https://doi.org/10.1073/PNAS.1119920109

Ciociola, A. A., Cohen, L. B., & Kulkarni, P. (2014). How Drugs are Developed and Approved by the FDA: Current Process and Future Directions. *The American Journal of Gastroenterology*, *109*. https://doi.org/10.1038/ajg.2013.407

Cleary, E. G., McNamee, L. M., de Boer, S., Holden, J., Fitzgerald, L., & Ledley, F. D. (2021). Comparing long-term value creation after biotech and non-biotech IPOs, 1997–2016. *PLOS ONE*, *16*(1). https://doi.org/10.1371/JOURNAL.PONE.0243813

Cooper, R. G. (2008). Perspective: The Stage-Gate® Idea-to-Launch Process—Update, What's New, and NexGen Systems*. *Journal of Product Innovation Management*, *25*(3), 213–232. https://doi.org/10.1111/J.1540-5885.2008.00296.X

Cowlrick, I. (2011). *Drug research and development case scenarios, development process, risks and benefits*. Dept. of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg.

Darrow, J. J., Avorn, J., & Kesselheim, A. S. (2020). FDA Approval and Regulation of Pharmaceuticals, 1983-2018. *JAMA*, *323*(2), 164–176. https://doi.org/10.1001/JAMA.2019.20288

de Bree, M., & Stoopendaal, A. (2020). De- and Recoupling and Public Regulation. *Organization Studies*, *41*(5), 599–620. https://doi.org/10.1177/0170840618800115

DeJonckheere, M., & Vaughn, L. M. (2019). Semistructured interviewing in primary care research: a balance of relationship and rigour. *Family Medicine and Community Health*, *7*(2). https://doi.org/10.1136/FMCH-2018-000057

DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics*, *47*, 20–33. https://doi.org/10.1016/J.JHEALECO.2016.01.012

Dolgos, H., Trusheim, M., Gross, D., Halle, J. P., Ogden, J., Osterwalder, B., Sedman, E., & Rossetti, L. (2016). Translational Medicine Guide transforms drug development processes: the recent Merck experience. *Drug Discovery Today*, *21*(3), 517–526. https://doi.org/10.1016/J.DRUDIS.2016.01.003

Donno, D., Boggia, R., Zunin, P., Cerutti, A. K., Guido, M., Mellano, M. G., Prgomet, Z., & Beccaro, G. L. (2016). Phytochemical fingerprint and chemometrics for natural food preparation pattern recognition: an innovative technique in food supplement quality control. *Journal of Food Science and Technology*, *53*(2), 1071. https://doi.org/10.1007/S13197-015-2115-6

Dou, J., Beitz, J., & Temple, R. (2019a). Development of Plant-Derived Mixtures as Botanical Drugs: Clinical Considerations. *AAPS Advances in the Pharmaceutical Sciences Series*, *32*, 245–264. https://doi.org/10.1007/978-3-030-11751-1_14

Dou, J., Beitz, J., & Temple, R. (2019b). Development of Plant-Derived Mixtures as Botanical Drugs: Clinical Considerations. In *AAPS Advances in the Pharmaceutical Sciences Series* (Vol. 32, pp. 245–264). Springer, Cham. https://doi.org/10.1007/978-3-030-11751-1_14

Drakeman, D., & Oraiopoulos, N. (2020a). The Risk of De-Risking Innovation: Optimal R&D Strategies in Ambiguous Environments. *California Management Review*, *62*(3), 42–63. https://doi.org/10.1177/0008125620915289

Drakeman, D., & Oraiopoulos, N. (2020b). The Risk of De-Risking Innovation: Optimal R&D Strategies in Ambiguous Environments. *California Management Review*, *62*(3), 42–63. https://doi.org/10.1177/0008125620915289

Eisenhardt, K. M. (1989). Building Theories from Case Study Research. *Academy of Management Review*, *14*(4), 532–550. https://doi.org/10.5465/AMR.1989.4308385

Ekanayake, S., & Subramaniam, N. (2012). Nature, extent and antecedents of risk management in accounting, law and biotechnology firms in Australia. *Accounting, Accountability & Performance*, *17*(1/2), 23–47. https://www.proquest.com/docview/1124362318?pq-origsite=gscholar&fromopenview=true

Eringfeld, S. (2021). *Podcasting as a research method*. National Centre for Research Methods. https://www.ncrm.ac.uk/RMeF2021/programme/show.php?event=64

Etikan, I., & Bala, K. (2017). Sampling and sampling methods. *Biometrics & Biostatistics International Journal*, *5*(6). https://doi.org/10.15406/bbij.2017.05.00149

Fatima, N., & Nayeem, N. (2016). Toxic Effects as a Result of Herbal Medicine Intake. In M. L. Larramendy & S. Soloneski (Eds.), *Toxicology - New Aspects to This Scientific Conundrum*. IntechOpen. https://doi.org/10.5772/64468

FDA. (2020, September 21). *Current Good Manufacturing Practice (CGMP) Regulations | FDA*. https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations

FDA, CDER, Rajiv, & Shaw. (2016). *Botanical Drug Development Guidance for Industry*. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Francis, P. H. (1992). Research Technology Management. *Research Technology Management*, *35*(4), 23. https://doi.org/https://doi.org/10.1080/08956308.1992.11670830

Gans, J. S., & Stern, S. (2003). The product market and the market for "ideas": commercialization strategies for technology entrepreneurs. *Research Policy*, *32*, 333–350. http://www.mbs.edu/home/jgans/research.htm

Gibbs, G. R. (2018). 4 Thematic coding and categorizing. In *Analyzing Qualitative Data* (Vol. 6). Sage. https://doi.org/10.4135/9781849208574

Godener, A., & Söderquist, K. E. (2004). Use and impact of performance measurement results in R&D and NPD: an exploratory study. *R&D Management*, *34*(2), 191–219. https://doi.org/10.1111/J.1467-9310.2004.00333.X

Graves, S. B. ;, Ringuest, J. L. ;, & Case, R. H. (2000). Formulating Optimal R&D Portfolios. *Research Technology Management*, *43*(3), 47–51. https://www.proquest.com/docview/213805728/fulltextPDF/C6F70A7A080B494DPQ/1?accountid=8424

Haigney, S. (2016). Nurturing the Relationship Between Industry and Regulators. *Pharmaceutical Technology*, *40*(12). https://www.pharmtech.com/view/nurturing-relationship-between-industry-and-regulators-0

Hautly, L. (2019). *Epistemological Perspectives In Qualitative Research* . Dr. Lisa Hautly . https://lisahautly.com/blog/epistemological-perspectives-in-qualitative-research

Healy, J. (2016). Improving health care safety and quality: Reluctant regulators. *Improving Health Care Safety and Quality: Reluctant Regulators*, 1–328. https://doi.org/10.4324/9781315588049/IMPROVING-HEALTH-CARE-SAFETY-QUALITY-JUDITH-HEALY

Hernández-Cuevas, C. (2007). Collaborative Innovation: The future of BioPharma. *J. Technol. Manag. Innov*, *2*(3). http://www.bionexa.org

Hine, D., & David, C. (2007). *Innovative Methodologies in Enterprise Research*. Edward Elgar Publishing. https://books.google.co.nz/books?hl=en&lr=&id=h6MKj0T1Lr8C&oi=fnd&pg=PR4&dq=Hine,+D.,+%26+Carson,+D.+(2007).+Innovative+methodologies+in+enterprise+research.+Cheltenham,+United+Kingdom:+Edward+Elgar+Publishing.&ots=1gDKRfDS_P&sig=NR_uZZQzL1lNTK1vUtizXznA-yM&redir_esc=y#v=onepage&q&f=false

Hoffman, F. A. (2015). Botanicals as "new" drugs: US development. *Epilepsy & Behavior*, *52*, 338–343. https://doi.org/10.1016/J.YEBEH.2015.07.028

Hooper, C. L. (2008). *Pharmaceuticals: Economics and Regulation* . The Concise Encyclopedia of Economics. https://www.econlib.org/library/Enc/PharmaceuticalsEconomicsandRegulation.html

Huang, X., Soutar, G. N., & Brown, A. (2002). New product development processes in small and medium-sized enterprises: Some Australian evidence. *Journal of Small Business Management*, *40*(1), 27–42. https://doi.org/10.1111/1540-627X.00036

Hughes, J. P., Rees, S. S., Kalindjian, S. B., & Philpott, K. L. (2011). Principles of early drug discovery. *British Journal of Pharmacology*, *162*(6), 1239. https://doi.org/10.1111/J.1476-5381.2010.01127.X

Inspection/Enforcement Resources | FDA. (2022, January 10). https://www.fda.gov/drugs/pharmaceutical-quality-resources/inspectionenforcement-resources

Jekunen, A. (2014). Decision-making in product portfolios of pharmaceutical research and development-managing streams of innovation in highly regulated markets. *Drug Design, Development and Therapy*. https://doi.org/10.2147/DDDT.S68579

Jeong, T. Y., Park, B. K., Cho, J. H., Kim, Y. il, Ahn, Y. C., & Son, C. G. (2012). A prospective study on the safety of herbal medicines, used alone or with conventional medicines. *Journal of Ethnopharmacology*, *143*(3), 884–888. https://doi.org/10.1016/j.jep.2012.08.016

Kaplan, R. S. (2009). Risk Management and the Strategy Execution System. *Balanced Scorecard Report*, *11*(6), 1–6. www.thepalladiumgroup.com

Kaplan, R. S., & Norton, D. P. (2007). Mastering the Management System. *Harvard Business Review*, 1–17. www.hbrreprints.org

Kaplan, S., & Murray, F. (2010). Entrepreneurship and the construction of value in biotechnology. In *Technology and organization: Essays in honour of Joan Woodward* (pp. 1–47). Emerald Group Publishing Limited.

Kille, J. W. (2017). Regulatory Toxicology. In *A Comprehensive Guide to Toxicology in Nonclinical Drug Development* (2nd ed., pp. 499–539). Academic Press. https://doi.org/10.1016/B978-0-12-803620-4.00019-0

Kimko, H., & Pinheiro, J. (2015). Model-based clinical drug development in the past, present and future: a commentary. *British Journal of Clinical Pharmacology*, *79*(1), 108–116. https://doi.org/10.1111/BCP.12341

Knoess, W., & Wiesner, J. (2019). The Globalization of Traditional Medicines: Perspectives Related to the European Union Regulatory Environment. *Engineering*, *5*(1), 22–31. https://doi.org/10.1016/j.eng.2018.11.012

Laelago, T. (2018). Herbal Medicine . In P. F. Builders (Ed.), *Herbal medicine use during pregnancy: benefits and untoward effects.* (pp. 103–120). IntechOpen. https://books.google.co.nz/books?hl=en&lr=&id=AGmQDwAAQBAJ&oi=fnd&pg=PA103&dq=increase+in+herbal+medicine+use&ots=mWMGmqQluO&sig=DaW2FUmqBYr7feJ2PrpBWFITMa8&redir_esc=y#v=onepage&q=increase%20in%20herbal%20medicine%20use&f=false

Lee, S. (2015). *Botanical Drug Development and Quality Standards*. https://pqri.org/wp-content/uploads/2015/10/01-PQRI-Lee-Botanicals-20151.pdf

Lee, S. L. (2019). A Totality-of-Evidence Approach to Ensuring Therapeutic Consistency of Naturally Derived Complex Mixtures. In *AAPS Advances in the Pharmaceutical Sciences Series* (Vol. 32, pp. 265–270). Springer Verlag. https://doi.org/10.1007/978-3-030-11751-1_15

Lincoln, J. (2012). Overview of the US FDA GMPs: Good Manufacturing Practice (GMP)/Quality System (QS) Regulation (21 CFR Part 820) . *Journal of Validation Technology*, *18*(3), 17–22.

https://www.proquest.com/docview/1054842716/fulltextPDF/4BC7E589D67D4184PQ/1?accountid=8424

Liu, Y., & Wang, M. W. (2008). Botanical drugs: Challenges and opportunities: Contribution to Linnaeus Memorial Symposium 2007. *Life Sciences*, *82*(9–10), 445–449. https://doi.org/10.1016/J.LFS.2007.11.007

Lokhande, J. N., & Lokhande, S. (2018). Botanical Drug Products and Rare Diseases. In J. N. Lokhande & Y. Pathak (Eds.), *Botanical Drug Products: Recent Developments and Market Trends* (pp. 187–201). CRC Press. https://doi.org/10.1201/B20896-9

Lux, W., Seiter, S., & Hinneburg, C. (2021, April 9). *Strategic Decision-Making in Early-Stage Drug Development and Lifecycle Management to Maximize a Drug's Lifetime Value*. Pharmaceutical Executive. https://www.pharmexec.com/view/strategic-decision-making-in-early-stage-drug-development-and-lifecycle-management-to-maximize-a-drug-s-lifetime-value

Lyles, M. A., Baird, I. S., Orris, J. B., & Kuratko, D. F. (1993). Formalized Planning in Small Business: Increasing Strategic Choices. *Journal of Small Business Management*, *31*, 38–50.

Malecki, S. L., Quinn, K. L., Zilbert, N., Razak, F., Ginsburg, S., Verma, A. A., & Melvin, L. (2019). Understanding the Use and Perceived Impact of a Medical Podcast: Qualitative Study. *JMIR Med Education*, *5*(2). https://doi.org/10.2196/12901

Malone, K., Hales, B., Chan, J., Love, M., & Rayner, J. (2008). Cloning an industry: Strategy typologies of Shanghai biotechnology companies. *Journal of Commercial Biotechnology*, *14*(1), 31–42. https://doi.org/10.1057/PALGRAVE.JCB.3050077/TABLES/2

Marcus, D. M., & Grollman, A. P. (2016). Toxicity of botanical medicines: An overlooked global health problem. *American Journal of Public Health*, *106*(1), 16–17. https://doi.org/10.2105/AJPH.2015.302937

Marsden, J., Bazzard, D., Breeze, K., De'ath, A., & Thwaites, A. (2020). *Rapid literature review on effective regulation: Implications for the Care Quality Commission*. 1–37.

McGrath, R. G., & Nerkar, A. (2004). Real options reasoning and a new look at the R&D investment strategies of pharmaceutical firms. *Strategic Management Journal*, *25*(1), 1–21. https://doi.org/10.1002/SMJ.358

Merriam, S. B. (2009). *Qualitative research: A guide to design and implementation*. John Wiley & Sons.

Milani, A., & Pathak, Y. (2018). Clinical Trial Management in Botanical Drug Products. In *Botanical Drug Products: Recent Developments and Market Trends* (pp. 245–266). Taylor & Francis Group. https://ebookcentral.proquest.com/lib/auckland/reader.action?docID=5601901&ppg=266

Miller, K. D., & Waller, H. G. (2003). Scenarios, Real Options and Integrated Risk Management. *Long Range Planning*, *36*(1), 93–107. https://doi.org/10.1016/S0024-6301(02)00205-4

Mintzberg, H. (1978). Patterns in Strategy Formation. *Management Science*, *24*(9), 934–948. https://doi.org/10.1287/MNSC.24.9.934

Mohs, R. C., & Greig, N. H. (2017). Drug discovery and development: Role of basic biological research. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *3*(4), 651–657. https://doi.org/10.1016/J.TRCI.2017.10.005

Molloy, P. L., & Johnson, L. W. (2016). Biotechnology, a strategic planning orphan: towards an effective strategy framework for biotechnology firms. *Journal of Commercial Biotechnology*, *22*(3), 118–125. https://doi.org/10.5912/JCB748

Moon, K., & Blackman, D. (2014). A Guide to Understanding Social Science Research for Natural Scientists. *Conservation Biology*, *28*(5), 1167–1177. https://doi.org/10.1111/COBI.12326/FULL

Muller, C. (2002). Strategic management: A tool for growth in the biotechnology sector. *Journal of Commercial Biotechnology*, *8*(3), 226–234.

Nielsch, U., Schäfer, S., Wild, H., & Busch, A. (2007). One target – multiple indications: a call for an integrated common mechanisms strategy. *Drug Discovery Today*, *12*(23–24), 1025–1031. https://doi.org/10.1016/J.DRUDIS.2007.10.004

Nielsen, V. L., & Parker, C. (2009). Testing responsive regulation in regulatory enforcement. *Regulation & Governance*, *3*(4), 376–399. https://doi.org/10.1111/J.1748-5991.2009.01064.X

Nieminen, O., Rahkamo, L., & Nordström, K. (2004). Biotechnology Regulation: Views of the Authorities, Investors, and Product Developers in Finland: *Drug Information Journal*, *38*(3), 253–264. https://doi.org/10.1177/009286150403800304

Noonan, K. (2021). *What's the difference between biotech and pharma?* . Alacrita Holdings Limited . https://www.alacrita.com/blog/whats-difference-biotech-pharma

Nwoko, O., & Drew, A. (2018). *Are Botanical Drugs, Herbal Medicinal Supplements, And Natural Product Drugs 505(b)(2)s, Too? | Camargo*. https://camargopharma.com/resources/blog/are-botanical-drugs-herbal-medicinal-supplements-and-natural-product-drugs-505b2s-too/

Ohanian, P. (2016, October 3). *Understanding The 4 Types Of FDA Inspection*. https://www.meddeviceonline.com/doc/understanding-the-types-of-fda-inspection-0001

Olson, M. K. (2014). Regulation of Safety, Efficacy, and Quality. In *Encyclopedia of Health Economics* (pp. 240–248). Elsevier. https://doi.org/10.1016/B978-0-12-375678-7.01202-5

WHO. (2003). *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants*. World Health Organization. https://www.google.co.nz/books/edition/WHO_Guidelines_on_Good_Agricultural_and/rFc0DgAAQBAJ?hl=en&gbpv=0

Pan, S. Y., Litscher, G., Gao, S. H., Zhou, S. F., Yu, Z. L., Chen, H. Q., Zhang, S. F., Tang, M. K., Sun, J. N., & Ko, K. M. (2014). Historical perspective of traditional indigenous medical practices: The current renaissance and conservation of herbal resources. *Evidence-Based Complementary and Alternative Medicine*, *2014*. https://doi.org/10.1155/2014/525340

Pan, S.-Y., Pan, S., Yu, Z.-L., Ma, D.-L., Chen, S.-B., Fong, W.-F., Han, Y.-F., & Ko, K.-M. (2010). New Perspectives on Innovative Drug Discovery: An Overview. In *J Pharm Pharmaceut Sci (www.cspsCanada.org)* (Vol. 13, Issue 3). www.cspsCanada.org

Patel, N. R., Ankolekar, S., Antonijevic, Z., & Rajicic, N. (2013). A mathematical model for maximizing the value of phase 3 drug development portfolios incorporating budget constraints and risk. *Statistics in Medicine*, *32*(10), 1763–1777. https://doi.org/10.1002/SIM.5731

Patton, M. Q. (1999). Enhancing the quality and credibility of qualitative analysis. *Health Services Research*, *34*(5 Pt 2), 1208.

Patwardhan, B., & Gautam, M. (2005). Botanical immunodrugs: scope and opportunities. *Drug Discovery Today*, *10*(7), 495–502. https://doi.org/10.1016/S1359-6446(04)03357-4

Petrovska, B. B. (2012). Historical review of medicinal plants' usage. *Pharmacognosy Reviews*, *6*(11), 1–5. https://doi.org/10.4103/0973-7847.95849

Pettigrew, A. M. (1990). Longitudinal field research on change: Theory and practice. *Organization Science*, *1*(3), 267–292. https://www.researchgate.net/profile/Andrew-

Pettigrew/publication/224952200_Longitudinal_Field_Research_on_Change_Theory_and_Practice/links/54dc82aa0cf2a7769d965d7c/Longitudinal-Field-Research-on-Change-Theory-and-Practice.pdf

Pisano, G. P. (2006). *Science Business: The Promise, the Reality and the Future of Biotech.* . Harvard Business School Press.

Plagnol, A. C., Rowley, E., Martin, P., & Livesey, F. (2009). Industry perceptions of barriers to commercialization of regenerative medicine products in the UK. *Http://Dx.Doi.Org/10.2217/Rme.09.21*, *4*(4), 549–559. https://doi.org/10.2217/RME.09.21

Radas, S., & Bozic, L. (2012). Overcoming Failure: Abandonments and Delays of Innovation Projects in SMEs. *Industry and Innovation*, *19*(8), 649–669. https://doi.org/10.1080/13662716.2012.739769

Rägo, L., & Santoso, B. (2008). Drug Regulation: History, Present and Future . In *Drug Benefits and Risks* (pp. 65–76).

Rao, S. K. (2022, February 3). *Managing R&D Risk*. Pharmaceutical Executive. https://www.pharmexec.com/view/managing-r-d-risk

Raz, T., & Michael, E. (2001). Use and benefits of tools for project risk management. *International Journal of Project Management*, *19*(1), 9–17. https://doi.org/10.1016/S0263-7863(99)00036-8

Razzaghi-Abyaneh, M., Rezaee, M.-B., Jaimand, K., & Shams-Ghahfarokhi, M. (2012). Plant Flora of Iran: History and Applications in Traditional Medicine. *Journal of Medicinal Plants and By-Products*, *1*, 1–2.

Reynoso, C. F. (2010). The Use of Case Studies in Preparing Postgraduate Dissertations on Small and Medium Sized Firms. *Review of Business & Finance Case Studies*, *1*(1), 81–94. http://ssrn.com/abstract=1881135

Roots, E. (2007). Making connections: The relationship between epistemology and research methods. *The Australian Community Psychologist*, *19*(1).

Rose, M., & Ceres, A. (2017, May). *Building A Productive Relationship With FDA Beyond The Science*. Pharmaceutical Online. https://www.pharmaceuticalonline.com/doc/building-a-productive-relationship-with-fda-beyond-the-science-0001

Rowley, J. (2002). Using case studies in research. *Management Research News*, *25*(1), 16–27. https://doi.org/10.1108/01409170210782990/FULL/XML

Saldana, J. (2021). *The Coding Manual for Qualitative Researchers* (J. Seaman, Ed.; 2nd ed.). Sage. http://emotrab.ufba.br/wp-content/uploads/2020/09/Saldana-2013-TheCodingManualforQualitativeResearchers.pdf

Schmidt, B. M., Ribnicky, D. M., Lipsky, P. E., & Raskin, I. (2007). Revisiting the ancient concept of botanical therapeutics. *Nature Chemical Biology*, *3*(7), 360–366. www.fda.gov/cder/Guidance/4592fnl.htm

Seimetz, D. (2017). The Key to Successful Drug Approval: An Effective Regulatory Strategy. In *Life Science Venturing* (pp. 139–165). Springer Gabler, Wiesbaden. https://doi.org/10.1007/978-3-658-06382-5_7

Seldon, T. (2011). Beyond patents: Effective intellectual properaty strategy in biotechnology. *Innovation: Management, Policy & Practice*, *13*(1), 55–61.

Shimasaki, C. D. (2009a). Significance of the Right Business Model and Managing Risk. In *The Business of Bioscience* (pp. 43–52). Springer, New York, NY. https://doi.org/10.1007/978-1-4419-0064-7_4

Shimasaki, C. D. (2009b). The Regulatory Process for Biotech Products. In *The Business of Bioscience* (pp. 205–221). Springer, New York, NY. https://doi.org/10.1007/978-1-4419-0064-7_13

Siggelkow, N. (2007). Persuasion with case studies. *Academy of Management Journal*, *50*(1), 20–24. https://doi.org/10.5465/AMJ.2007.24160882

Stake, R. E. (1995). *The Art of Case Study Research* . Sage. https://experts.illinois.edu/en/publications/the-art-of-case-study-research

Stavros, C., & Westberg, K. (2009). Using triangulation and multiple case studies to advance relationship marketing theory. *Qualitative Market Research*, *12*(3), 307–320. https://doi.org/10.1108/13522750910963827/FULL/XML

Sun, Y., & Qian, J. (2021). Botanical drug clinical trial: Common issues and future options. *Acta Pharmaceutica Sinica B*, *11*(1), 300–303. https://doi.org/10.1016/J.APSB.2020.08.003

Tamayo, C., & Hoffman, F. A. (2017). Botanical Regulation: Comparison of the United States and Canada. *Pharmaceutical Regulatory Affairs: Open Access*, *06*(01). https://doi.org/10.4172/2167-7689.1000189

Teece, D. J. (1986). Profiting from technological innovation: Implications for integration, collaboration, licensing and public policy. *Research Policy*, *15*(6), 285–305. https://doi.org/10.1016/0048-7333(86)90027-2

Thakkar, S., Anklam, E., Xu, A., Ulberth, F., Li, J., Li, B., Hugas, M., Sarma, N., Crerar, S., Swift, S., Hakamatsuka, T., Curtui, V., Yan, W., Geng, X., Slikker, W., & Tong, W. (2020). Regulatory landscape of dietary supplements and herbal medicines from a global perspective. *Regulatory Toxicology and Pharmacology*, *114*. https://doi.org/10.1016/j.yrtph.2020.104647

Thurmond, V. A. (2001). The Point of Triangulation. *Journal of Nursing Scholarship*, *33*(3), 253–258. https://doi.org/10.1111/J.1547-5069.2001.00253.X

U.S. Congress. (1934). *Federal Food, Drug, and Cosmetic Act (FD&C Act) | FDA*. https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act

van Norman, G. A. (2016). Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs. *JACC: Basic to Translational Science*, *1*(3), 170–179. https://doi.org/10.1016/J.JACBTS.2016.03.002

van Wyk, A. (2005). *EVALUATION OF GUIDELINES FOR CLINICAL TRIALS OF TRADITIONAL PLANT MEDICINES*.

Vanderbyl, S., & Kobelak, S. (2008). Risk management for the biotechnology industry: A Canadian perspective. *Journal of Commercial Biotechnology* , *14*(2), 140. https://doi.org/10.1057/palgrave.jcb.3050087

Vanherweghem, J. L., Depierreux, M., Tielemans, C., Abramowicz, D., Dratwa, M., Jadoul, M., Richard, C., Vandervelde, D., Verbeelen, D., Vanhaelen-Fastre, R., & Vanhaelen, M. (1993). Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *The Lancet*, *341*(8842), 387–391. https://doi.org/10.1016/0140-6736(93)92984-2

Vartanian, T. P. (2010). *Secondary data analysis*. Oxford University Press.

Verma, A. S., Agrahari, S., Rastogi, S., & Singh, A. (2011). Biotechnology in the Realm of History. *Journal of Pharmacy and Bioallied Sciences*, *3*(3), 321. https://doi.org/10.4103/0975-7406.84430

Woiceshyn, J., & Hartel, D. (1996). Strategies and performance of Canadian biotechnology firms: an empirical investigation. *Technovation*, *16*(5), 231–266. https://doi.org/10.1016/0166-4972(95)00066-6

Wong, J. (2011). From Mitigating Risk to Managing Uncertainty. In *Betting on Biotech: Innovation and the Limits of Asia's Developmental State* (1st ed., pp. 16–42). Cornell University Press. http://ebookcentral.proquest.com/lib/auckland/detail.action?docID=3138253.

Wouters, O. J., McKee, M., & Luyten, J. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA*, *323*(9), 844–853. https://doi.org/10.1001/JAMA.2020.1166

Wright, S. (2021). *The Development of Plant-Based Medicines for Prescription | Technology Networks*. https://www.technologynetworks.com/drug-discovery/blog/the-development-of-plant-based-medicines-for-prescription-346230

Wu, C., Lee, S.-L., Taylor, C., Li, J., Chan, Y.-M., Agarwal, R., Temple, R., Throckmorton, D., & Tyner, K. (2020). Scientific and Regulatory Approach to Botanical Drug Development: A U.S. FDA Perspective. *Journal of Natural Products*, *83*(2), 552–562. https://doi.org/10.1021/ACS.JNATPROD.9B00949

Wu, K. M., DeGeorge, J. G., Atrakchi, A., Barry, E., Bigger, A., Chen, C., Du, T., Freed, L., Geyer, H., Goheer, A., Jacobs, A., Jean, D., Rhee, H., Osterberg, R., Schmidt, W., & Farrelly, J. G. (2000). Regulatory science: a special update from the United States Food and Drug Administration: Preclinical issues and status of investigation of botanical drug products in the United States. *Toxicology Letters*, *111*(3), 199–202. https://doi.org/10.1016/S0378-4274(99)00152-6

Yin, R. K. (2009). *Case Study Research: Design and Methods* (Vol. 5). Sage. https://books.google.co.nz/books?hl=en&lr=&id=FzawIAdilHkC&oi=fnd&pg=PR1&dq=Yin,+R.+K.+(2014).+Case+study+research:+Design+and+methods+(5th+ed.).&ots=l_1X3hpS0o&sig=7ztqDrT6pWbn_fr1YLd4y0Ym0Xg&redir_esc=y#v=onepage&q&f=false

Yuan, R., & Lin, Y. (2000). Traditional Chinese medicine: an approach to scientific proof and clinical validation. *Pharmacology & Therapeutics*, *86*(2), 191–198. https://doi.org/10.1016/S0163-7258(00)00039-5

Zhang, A. L., Changli Xue, C., & Fong, H. H. S. (2011). *Integration of Herbal Medicine into Evidence-Based Clinical Practice: Current Status and Issues* (2nd ed.). CRC Press/Taylor & Francis, Boca Raton (FL). http://europepmc.org/books/NBK92760

Zhou, X., Seto, S. W., Chang, D., Kiat, H., Razmovski-Naumovski, V., Chan, K., & Bensoussan, A. (2016). Synergistic effects of Chinese herbal medicine: A comprehensive review of methodology and current research. *Frontiers in Pharmacology*, *7*(JUL), 201. https://doi.org/10.3389/FPHAR.2016.00201/BIBTEX